CONTENTS

The American Journal of Medicine

VOL. VIII JUNE, 1950 No. 6

Editorial

The Clinical Laboratory and Training for Internal Medicine . ROY H. TURNER 689

Clinical Studies

Symptom Patterns of the Hyperventilation Syndrome . . . RAYMOND L. RICE 691

Dr. Rice in this enthusiastic and interesting paper calls attention to a syndrome which is important in private and clinic practice and which is all too often misinterpreted.

Pulmonary Hypertension in Chronic Pulmonary Emphysema
CRAIG W. BORDEN, RUSSELL H. WILSON, RICHARD V. EBERT AND HERBERT S. WELLS 701

Direct measurements by catheterization technics showed a significant elevation of pulmonary arterial diastolic pressure in twenty-four patients with emphysema, indicating increased vascular resistance in the pulmonary bed.

The Role of Nitrogen Mustard Therapy in the Treatment of Lymphomas and Leukemias
CHARLES L. SPURR, TAYLOR R. SMITH, MATTHEW BLOCK AND LEON O. JACOBSON 710

An analysis of long-term results of nitrogen mustard therapy in ninety-five cases of lymphomas and leukemias, with discussion of the proper relation of chemotherapy to radiotherapy. The results, in general, conform with previous experience.

Hypercalcemia in Osteolytic Metastatic Cancer of the Breast
ALFRED J. SWYER, CAPT. JAMES S. BERGER, HAROLD M. GORDON AND DANIEL LASZLO 724

An interesting study of the incidence and clinical consequences of hypercalcemia in patients with extensive osteolytic metastases from breast carcinoma.

Use of Paraffin-embedding Methods in the Cytologic Study of Various Bodily Secretions . . . . . N. R. BOTHEREAU 733

A generally applicable method for obtaining specimens of various bodily secretions suitable for cytologic study and cancer detection. The photomicrographs are striking.

Contents continued on page 5

Widen the scope of routine office examinations

CLINITEST

(Brand) Reagent Tablets

for detection of urine-sugar

Prompt detection means better prognosis in diabetes. This makes a routine search for urine-sugar integral to every office examination. For this purpose, *Clinitest* (Brand) Reagent Tablets are exceptionally useful. The test is simple, rapid and reliable. No external heating is needed. Set, Laboratory Outfit, and Refills of 24 and 36 tablets.

ACETEST

(Brand) Reagent Tablets

for detection of acetone bodies

Detection of ketosis in diabetes—and many other conditions in which acidosis may occur—is facilitated for the physician by *Acetest* (Brand) Reagent Tablets. This unique spot test swiftly and easily detects acetone bodies. The sensitivity is 1 part in 1,000. Bottles of 100 and 1000.

HEMATEST

(Brand) Reagent Tablets

for detection of occult blood

Occult blood in feces, sputum or urine is often the earliest evidence of pathologic processes otherwise unsuspected. Determination of blood (present as 1 or more parts in 20,000) becomes a practical part of office routine with *Hematest* (Brand) Reagent Tablets—accurate, quick, and convenient. Bottles of 60 and 500.

AMES COMPANY, INC · ELKHART, INDIANA

CONTENTS

The American Journal of Medicine

VOL. VIII JUNE, 1950 No. 6

Contents continued from page 3

Arthro-onychodysplasia. Hereditary Syndrome Involving Deformity of Head of Radius, Absence of Patellas, Posterior Iliac Spurs, Dystrophy of Finger Nails
A. M. BRIXEY, Jr. AND RICHARD M. BURKE 738

An interesting account of a bizarre hereditary syndrome.

Review

The Thermal Coagulation Point of Blood Serum . . . GEORGE B. JERZY GLASS

I. Method and Clinical Interpretation 745

II. Significance of the Principle of Defective Thermal Coagulation for Diagnosis of Cancer 755

III. Correlation with Serum Proteins, Sedimentation Rate and Weltmann Reaction . 759

Recent interest in the effect of disease, particularly cancer, on the heat coagulation properties of serum lends timeliness to this report. Dr. Glass has made an extensive study of this subject, revealing the inadequacies of the procedure as a test for cancer but bringing out many new points of intrinsic interest and possible application.

Seminars on Cancer Research

Present Status of Clinical Cancer Chemotherapy
DAVID A. KARNOFSKY AND JOSEPH H. BURCHENAL 767

The authors contribute a realistic and factual estimate of the present status of chemotherapy in clinical cancer and of its relation to radiotherapy and surgery. The successes of chemotherapy to date are few and usually of temporary character but represent a definite advance, with prospects of further tangible results in the future.

Clinic on Psychosomatic Problems

Ulcerative Colitis 789

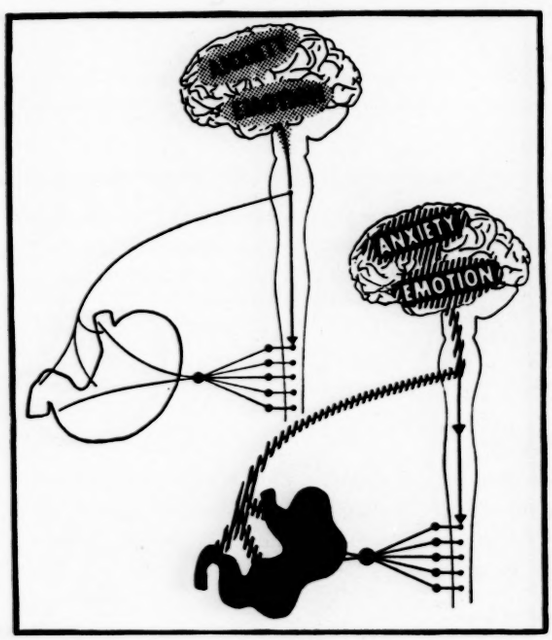
Clinic on Psychosomatic Problems (Massachusetts General Hospital)—This clinic expresses a conservative and restrained point of view regarding the role of psychogenic factors in the causation of ulcerative colitis and the role of the psychiatrist in its management. The advantages of a balanced medical, psychiatric and surgical therapeutic program are stressed.

Contents continued on page 7

". . . about 50% of the patients who consult the general practitioner have complaints for which there is no discoverable physical or organic cause."[1]

Emotional response and adaptation to stress of the times play major roles in the increase of functional disorders. Exaggerated emotional response may produce somatic symptoms such as vague pains referred to various organs. Nausea, headache, cardiac and gastrointestinal distress are often presenting complaints. Diagnosis is usually easy in these cases because the number and variety of symptoms are not corroborated by physical findings. *Yet, these patients are seriously ill and merit attention and relief. Recent research has indicated that functional disturbances may develop into organic disease if long continued*[2]. In functional disorders, response to stress is effected via both branches of the autonomic nervous system. Therefore, treatment consists, where possible, in removal of the emotogenic factor (practical psychotherapy) and the "partial blockade" of the efferent autonomic pathways.

The family physician is well qualified to help these patients since he is most often aware of the environmental circumstances. His advice and guidance will do much to achieve the desired change in activities and habits and will help the patient to avoid "unhealthy situations".



Medical treatment is also essential in most cases. Controlled sedation of the entire autonomic nervous system accelerates recovery. This is accomplished by simultaneous administration of Bellafoline (cholinergic inhibitor), ergotamine tartrate (adrenergic inhibitor) and phenobarbital (central sedative).

Bellergal is a time tested preparation for administration in a wide variety of functional disorders. Bellergal inhibits the transmission of autonomic impulses without completely blocking organ function. This type of "mild sedation" will permit the patient to carry on daily activities while "taking stock of his difficulties". Karnosh and Zucker[3] state that, "Probably the best medication for all neurovegetative disorders is a combination of: (a) Bellafoline... (b) Ergotamine tartrate... (c) Phenobarbital... A good commercial preparation of these ingredients is a tablet called bellergal... The adult dose of bellergal is 3 or 4 tablets daily."

BIBLIOGRAPHY

1. WILLIAMS, V. P.: Medical Progress: Psychiatry, New England J. Med. *236:* 322-326 (Feb. 27) 1947.
2. NAIA, J. A.: Psyche and Somatic Disorders, Neurobiologia *9:* 269-278, 1946: Psychosom. Med. *10:* 120 (March-April) 1948.
3. KARNOSH, L. J. and ZUCKER, E. N.: A Handbook of Psychiatry, St. Louis, The C. V. Mosby Company, 1945, p. 248.

Brochures available on request:
"The A.N.S. and Functional Disorders."
"The Menopause Needs More Than Hormones."
"The A.N.S. and—Gastrointestinal Disorders—Cardiac Neuroses—Gynecological Problems—Anxiety States." (A series)

Sandoz Pharmaceuticals
DIVISION OF SANDOZ CHEMICAL WORKS, INC.
68 CHARLTON STREET, NEW YORK 14, NEW YORK

CONTENTS

The American Journal of Medicine

VOL. VIII JUNE, 1950 No. 6

Contents continued from page 5

Clinico-pathologic Conference

Penicillin-resistant Subacute Bacterial Endocarditis 794

Clinico-pathologic Conference (Washington University School of Medicine)—This interesting case of subacute bacterial endocarditis served as a springboard for an instructive discussion of this disease when caused by penicillin-resistant enterococci. Aureomycin proved to be ineffective in this instance.

Special Feature

American Federation for Clinical Research—Abstracts of Papers Presented at the Seventh Annual Meeting of the Midwestern Section Held in Chicago, November 3, 1949 805

Case Reports

Clinical Aspects of Ochronosis. With Report of a Case
EUGENE L. COODLEY AND ANTHONY J. GRECO 816

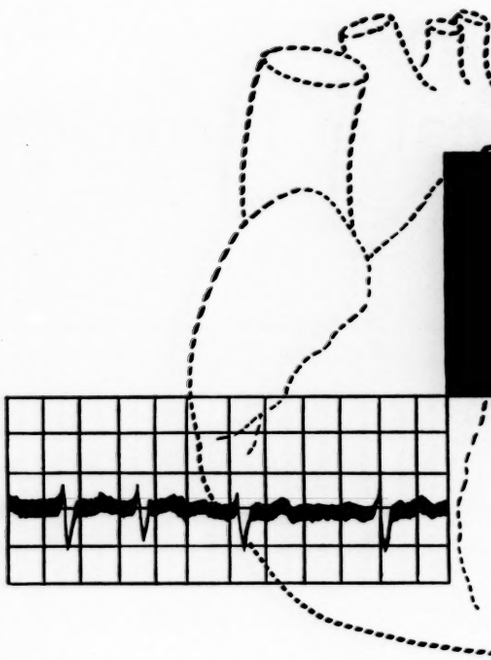
An interesting case report of ochronosis, with autopsy findings.

Sweat Test Simplified for Clinical Use . . ALAN LESLIE AND MELVIN H. LEVIN 823

The authors describe a simple method for obtaining thermal sweat uncontaminated by external sources of electrolytes and suitable for study of this phase of adrenal cortical activity.

Author Index to Volume VIII 826

Subject Index to Volume VIII 827



DIGOXIN

'B.W.&Co.'

A pure crystalline glycoside derived from Digitalis lanata

Digoxin has been selected for use in fundamental studies on the hemodynamics of heart failure[1] and as a glycoside of choice for practical clinical treatment of heart failure[2] and auricular flutter.[3]

Harvey et al.[1] stated that in patients with left-sided heart failure "Digoxin produced a significant rise in cardiac output and stroke volume accompanied by a decrease in pulmonary arterial pressure."

Schaaf et al.[3] have concluded from their studies at the Massachusetts General Hospital that in the treatment of auricular flutter "digoxin was preferred to digitoxin or digitalis for this purpose because of its greater margin of safety."

1. Harvey, R.M.; Ferrer, M.I.; Cathcart, R.T.; Richards, D.W., and Cournand, A.: Some Effects of Digoxin upon the Heart and Circulation in Man: Am. J. Med. 7:439 (Oct.) 1949.

2. Batterman, R.G., and DeGraff, A.C.: Comparative Study on the Use of the Purified Digitalis Glycosides, Digoxin, Digitoxin, and Lanatoside C, for the Management of Ambulatory Patients with Congestive Heart Failure: Am. Heart J. 34:663 (Nov.)1947.

3. Schaaf, R.S.; Hurst, J.W., and Williams, C.: The Management of Auricular Flutter: Med. Clin. N. Am. p. 1255 (Sept.) 1949.

BURROUGHS WELLCOME & CO. (U.S.A.) INC.

TUCKAHOE 7, NEW YORK

BOOK SECTION

"Reading is to the mind what exercise is to the body."

—Addison

26
ESSAYS COVERING THE LATEST IN MEDICAL RESEARCH

JUST PUBLISHED

by

32
OUTSTANDING CONTRIBUTORS

Thomas F. Anderson • F. M. Burnet • Harry M. Rose • John R. Paul • Lancelot Hogben • M. F. Ashley Montague • Elvin A. Kabat • W. E. Knox • Richard O. Roblin, Jr. • D. D. Woods • D. Shemin • I. London • J. P. Peters • Robert F. Pitts • Dickinson W. Richards, Jr. • Paul Gyorgy • Ephraim Shorr • B. W. Zweifach • R. F. Furchgott • S. Howard Armstrong, Jr. • Maxwell M. Wintrobe, • C. P. Rhoads • Alvin F. Coburn • Luis F. Leloir • Richard Day • Theodore H. Ingalls • Howard Mason • Dorothy Andersen • I. S. Ravdin • Judah Ebin • Karl Menninger • Abel Wolman.

"The individual articles go further than the ordinary scientific paper in expressing the authors' feeling about their work; this, along with generally good bibliographies, makes the essays eminently useful for research men in the same field. Secondly, many of the papers may serve as an introduction for scientists to fields outside of their own."

THE NEW YORK TIMES

Those changes that are constantly taking place in the field of medical research are discussed by various outstanding representatives in the fields of chemotherapy, therapeutics, physiology, epidemiology, microbiology, anthropology, and allied sciences. Written in non-technical language, these essays cover the most outstanding developments and achievements in each field to date and then indicate the most likely paths of future progress.

Edited by David E. Green, Ph.D. and W. Eugene Knox, M.D.,
492 pp. $6.50

THE MACMILLAN COMPANY
60 Fifth Ave., New York 11, N.Y.

Please send me on approval_____copies of Green:
RESEARCH IN MEDICAL SCIENCE–$6.50

Name_____

Address_____

HARRISON:

Principles of Internal Medicine

ANOTHER BLAKISTON ACHIEVEMENT

MORE and more doctors are finding that the Blakiston colophon on a medical book, text or reference means "Authority which imparts confidence."

Principles of Internal Medicine is the newest addition to the Blakiston line of outstanding medical books.[1] For the practitioner and the teacher, this is the first textbook to thoroughly integrate the pre-clinical sciences with clinical medicine. It is written by a distinguished staff of five editors: T. R. Harrison, Professor and Chairman of Department of Internal Medicine, Southwestern Medical College; M. M. Wintrobe, Professor and Head, Department of Medicine, University of Utah College of Medicine; Paul B. Beeson, Professor and Chairman of the Department of Medicine, Emory University School of Medicine; William H. Resnik, Stamford, Conn.; and George W. Thorn, Hersey Professor of the Theory and Practice of Physic, Harvard Medical School, and 53 authorities.

Arranged in seven parts, the first five—Cardinal Manifestations of Disease, Physiologic Considerations, Reactions to Stress and to Antigenic Substances, Metabolic and Endocrine Disorders, and Disorders Due to Chemical and Physical Agents—cover the functional approach. The last two deal with specific diseases: Diseases Due to Biologic Agents, and Diseases of Organ Systems.

To you who practice or teach medicine as an art and science, who try to integrate the pre-clinical sciences with clinical medicine . . . this new book will be of great interest. Why not send for your copy now!

245 Illustrations, $12.00

ANNOUNCING THE NEWEST BOOK OF INTERNAL MEDICINE

[1] **Blakiston's New Gould Medical Dictionary**—the first new medical dictionary in 38 years. 30,000 sold since publication. (Aug., 1949)

ACTH—The Proceedings of the First Clinical ACTH Conference—the basic information on its clinical use. (*Time Magazine*, April 10)

This coupon will bring you any of these Blakiston firsts.

The Blakiston Company
1012 Walnut Street
Philadelphia 5, Pa.

THE BLAKISTON COMPANY, 1012 Walnut Street, Philadelphia 5, Pa.

Please send the items checked; my check is enclosed ☐; charge my account ☐. It is understood that you will credit my account in full for any books that I wish to return within 10 days.

☐ Harrison's Principles of Internal Medicine—$12.00 ☐ Blakiston's New Gould Medical Dictionary ☐ school edition—$8.50 ☐ professional edition—$10.75 ☐ deluxe edition—$13.50 ☐ The Proceedings of the First Clinical ACTH Conference—$5.50

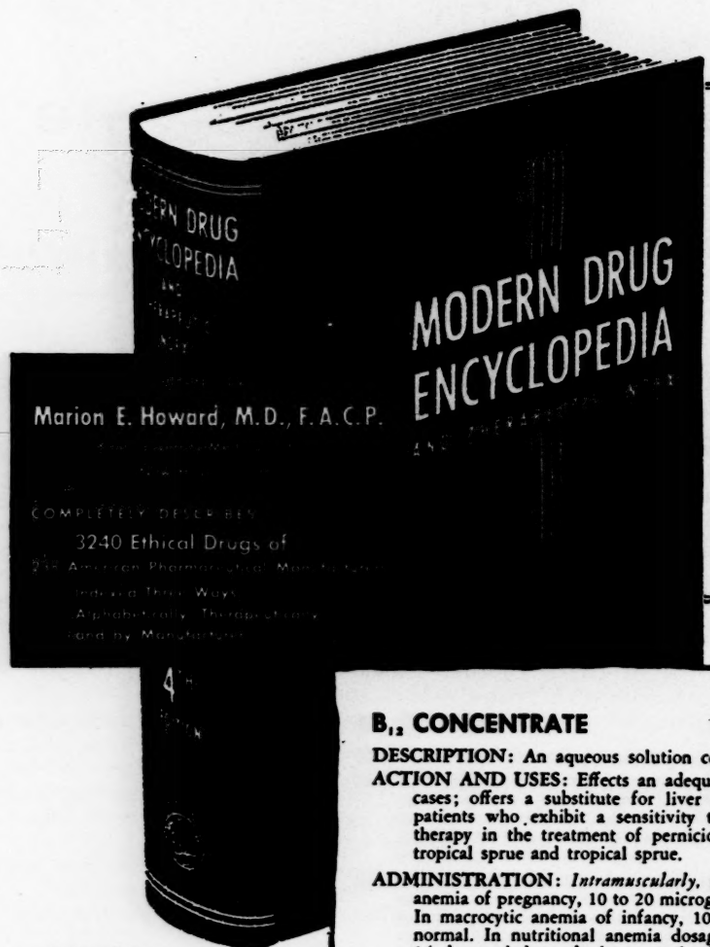
NAME_____ ADDRESS_____

CITY_____ ZONE_____ STATE_____

AJM 6-50

A MEDICAL BEST SELLER!

SECOND PRINTING



1949 Edition
Bound in Red Fabricoid
1,200 pages, Size 2" x 6" x 9"
Price Postpaid $12 U.S.A.—
$14 Foreign

Doctors' Comments

"Please accept my congratulations on your excellent publication on Modern Drugs." K.S.G., M.D., Durham, N. C.

"I am finding it very useful." L.I.Y., M.D., Winona, Minn.

"Put my name down to send me a new one every time it comes off the press." D.H.A., M.D., Memphis, Tenn.

"I think this is one of the best publications in print." W.S., M.D., Augusta, Ga.

Typical Description

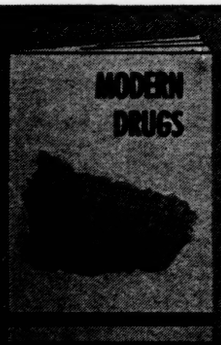
B_{12} CONCENTRATE ***Hematopoietic*** **(Armour)**

DESCRIPTION: An aqueous solution containing 10 micrograms of vitamin B_{12} per cc.

ACTION AND USES: Effects an adequate hematopoietic response in pernicious anemia cases; offers a substitute for liver therapy in the treatment of pernicious anemia patients who exhibit a sensitivity to liver extract. An important adjunct to liver therapy in the treatment of pernicious anemia, nutritional macrocytic anemia, non-tropical sprue and tropical sprue.

ADMINISTRATION: *Intramuscularly*, preferably in the gluteal muscle. In macrocytic anemia of pregnancy, 10 to 20 micrograms once a week until termination of pregnancy. In macrocytic anemia of infancy, 10 to 20 micrograms until blood count returns to normal. In nutritional anemia dosage may vary from 6 to 100 micrograms over a 14 day period to obtain an optimal response. In most pernicious anemia cases 25 micrograms per week results in an optimal response.

SUPPLY: B_{12} CONCENTRATE—Vials, rubber-capped, 10 cc.



Drug Publications, Inc.
49 West 45th St., New York 19, N. Y.

Enclosed is the sum of twelve dollars ($12 U.S.A.) for which please send me postpaid the new Fourth Edition of the MODERN DRUG ENCYCLOPEDIA AND THERAPEUTIC INDEX AND MODERN DRUGS.

Name.....

Address.....

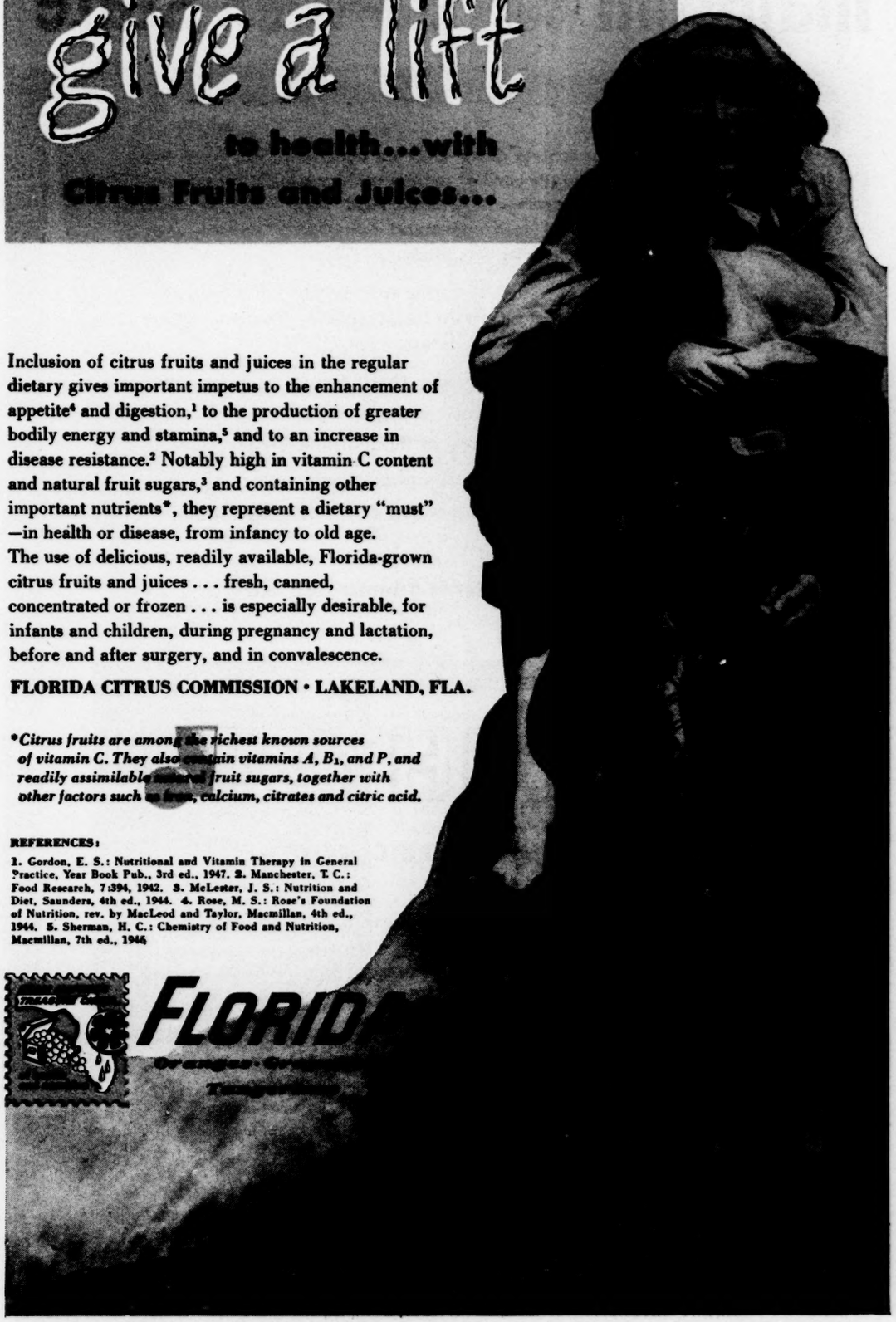
City..... Zone..... State.....

U.S.A. $12 Foreign $14

END OF BOOK SECTION

give a lift

to health...with Citrus Fruits and Juices...



Inclusion of citrus fruits and juices in the regular dietary gives important impetus to the enhancement of appetite[4] and digestion,[1] to the production of greater bodily energy and stamina,[5] and to an increase in disease resistance.[2] Notably high in vitamin C content and natural fruit sugars,[3] and containing other important nutrients*, they represent a dietary "must" —in health or disease, from infancy to old age.

The use of delicious, readily available, Florida-grown citrus fruits and juices . . . fresh, canned, concentrated or frozen . . . is especially desirable, for infants and children, during pregnancy and lactation, before and after surgery, and in convalescence.

FLORIDA CITRUS COMMISSION • LAKELAND, FLA.

**Citrus fruits are among the richest known sources of vitamin C. They also contain vitamins A, B_1, and P, and readily assimilable natural fruit sugars, together with other factors such as iron, calcium, citrates and citric acid.*

REFERENCES:

1. Gordon, E. S.: Nutritional and Vitamin Therapy in General Practice, Year Book Pub., 3rd ed., 1947. 2. Manchester, T. C.: Food Research, 7:394, 1942. 3. McLester, J. S.: Nutrition and Diet, Saunders, 4th ed., 1944. 4. Rose, M. S.: Rose's Foundation of Nutrition, rev. by MacLeod and Taylor, Macmillan, 4th ed., 1944. 5. Sherman, H. C.: Chemistry of Food and Nutrition, Macmillan, 7th ed., 1946

FLORID

maintain edema-free state

Only one or two tablets daily—plus an occasional injection—are needed to maintain the cardiac patient at "dry weight" employing Tablets MERCUHYDRIN® with Ascorbic Acid. Some patients—freed of accumulated fluid with parenteral meralluride sodium—may be kept edema-free on tablets alone.

Tablets MERCUHYDRIN with Ascorbic Acid permit daily fluid control with a minimum of injections facilitating the frequent-dosage schedule of modern diuretic therapy.

ideal for ambulant patients and those who cannot be given frequent injections.

well tolerated when prescribed in the recommended dosage.

effective in producing mild, sustained diuretic action.

convenient—the oral is the safest and most convenient route.

Keep your cardiac patients edema-free with . . .

Tablets

MERCUHYDRIN®

WITH ASCORBIC ACID

dosage: One to two tablets daily—morning or evening—preferably after meals.

available: Bottles of 100. Each tablet contains meralluride 60 mg. and ascorbic acid 100 mg.

Lakeside Laboratories, INC., MILWAUKEE 1, WISCONSIN

UNRETOUCHED PHOTOGRAPHS—SAME CHILD

Right leg: 40 min. after injection of 300 cc. saline solution without Hydase. Note intense swelling.

Left leg: 40 min. after injection of 500 cc. saline solution with Hydase. Swelling is very slight.

Efficiency

Safety

Patient-comfort

Wyeth

In hypodermoclysis . . .

HYDASE has proved a remarkably efficient aid to hypodermoclyses of saline and nutrient solutions. Ideally suited for use when it is difficult or impractical to inject into veins.

In local anesthesia . . .

Hydase facilitates nerve block anesthesia because it diffuses the anesthetic to the desired area; no need to inject directly into the nerve.

HYDASE*

Lyophilized Hyaluronidase

is safe: nontoxic, nonantigenic, nonallergenic. Supplied in vials of 150 and 500 TR (Turbidity-reducing) units.

Descriptive literature to physicians on request

*Trade Mark

Wyeth Incorporated, Philadelphia 3, Pa.

emotional equilibrium for the geriatric patient

Thousands of doctors know that BENZEBAR* allays the mental depression, apprehension and nervousness so frequently found in the elderly patient.

'Benzebar' is S.K.F.'s logical combination of Benzedrine* Sulfate and phenobarbital. It provides the unique improvement of mood of 'Benzedrine' Sulfate and the calming, soothing influence of phenobarbital. These two established agents work together to restore the elderly person's zest for life and living, to quiet his nervousness and, at the same time, to keep him from overdoing.

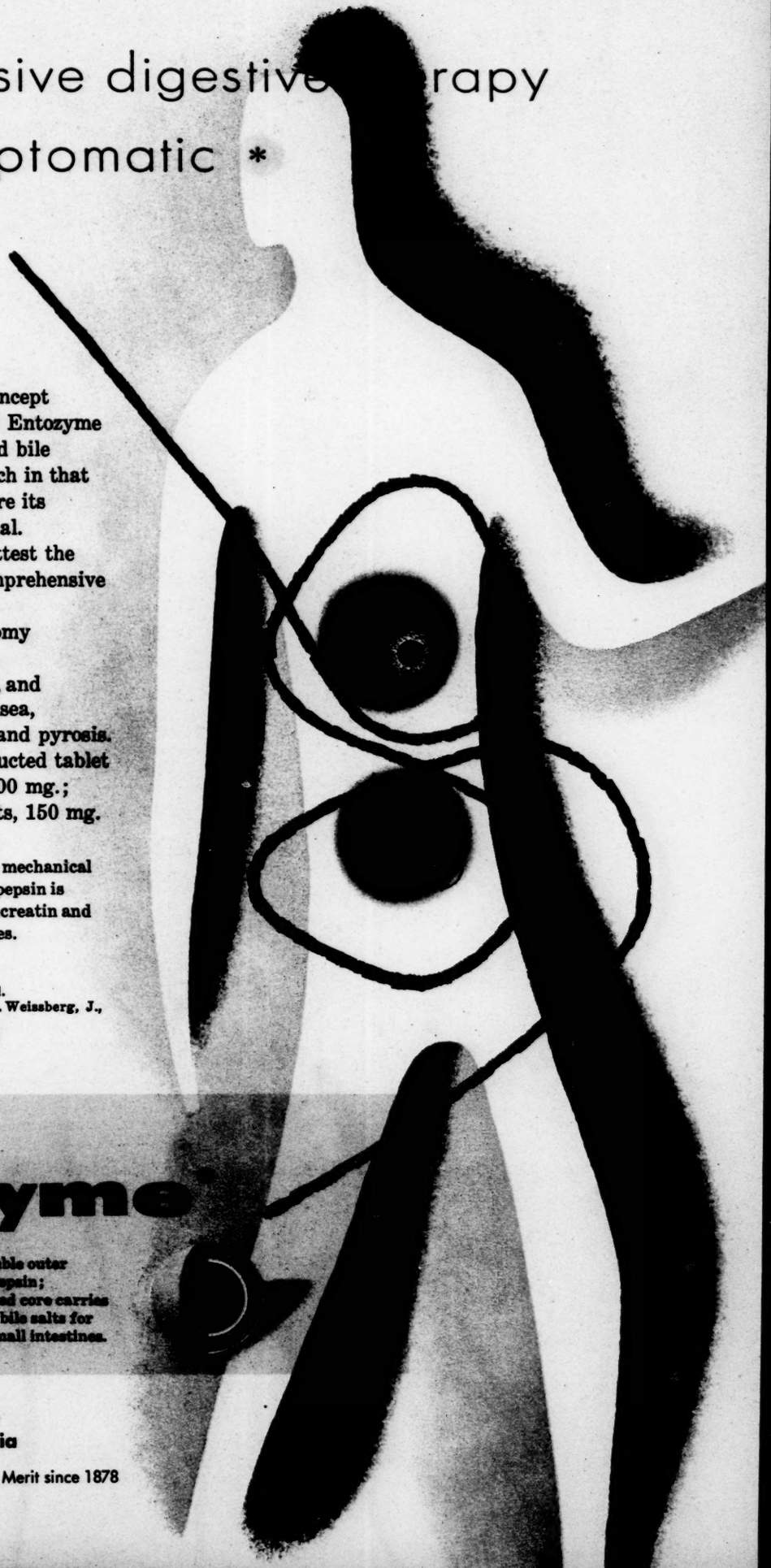
Each 'Benzebar' tablet contains: 'Benzedrine' Sulfate, N.N.R. (racemic amphetamine sulfate, S.K.F.), 5 mg.; phenobarbital, ¼ gr.

Smith, Kline & French Laboratories, Philadelphia

Benzebar for the depressed and nervous patient

*'Benzedrine' and 'Benzebar' T.M. Reg. U.S. Pat. Off.

comprehensive digestive therapy through peptomatic * action .....



Pioneering an entirely new concept of tablet construction, Robins' Entozyme releases pepsin, pancreatin and bile salts from a single tablet – each in that part of the digestive tract where its enzymatic action will be maximal. Controlled clinical studies[1,2] attest the remarkable efficacy of this comprehensive digestant therapy in chronic cholecystitis, post-cholecystectomy syndrome, infectious hepatitis, pancreatitis, chronic dyspepsia, and peptic ulcer; as well as in nausea, anorexia, belching, flatulence and pyrosis.

Formula: Each specially constructed tablet contains pancreatin, U.S.P., 300 mg.; pepsin, N.F., 250 mg.; bile salts, 150 mg.

* A coined word to describe the unique mechanical action of Entozyme Tablet, whereby pepsin is released only in the stomach, and pancreatin and bile salts only in the small intestines.

1. McGavack, T. H., and Klotz, S. D.: Bull. Flower Fifth Ave. Hosp., 9: 61, 1946. 2. Weissberg, J., et al.: Am. J. Digest Dis., 15: 332, 1948.

entozyme

Gastrically soluble outer shell contains pepsin; enterically coated core carries pancreatin and bile salts for release in the small intestines.

Robins

A. H. Robins Co., Inc.
Richmond 20, Virginia

Ethical Pharmaceuticals of Merit since 1878

Robins

A POSITIVE MEANS OF

Promoting Nutritional Adequacy

Whenever the need for dietary supplementation arises—as in anorexia, perverted food habits, during and following illness, and in gastrointestinal disease—the regular use of Ovaltine in milk can be of signal value. Taken daily, this well-rounded multiple dietary supplement gives virtual assurance of nutritional adequacy.

As indicated in the table, Ovaltine in milk provides virtually all essential nutrients in balanced, generous amounts. Its protein is biologically complete. It supplies not only B complex vitamins, but also vitamins A and D as well as ascorbic acid and essential minerals.

The delightful taste and easy digestibility of this food beverage is relished by patients, hence the recommended three glassfuls daily are taken without resistance.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.

Ovaltine

Three servings of Ovaltine, each made of ½ oz. of Ovaltine and 8 oz. of whole milk, provide:*

PROTEIN	32 Gm.	VITAMIN A	3000 I.U.
FAT	32 Gm.	VITAMIN B_1	1.16 mg.
CARBOHYDRATE	65 Gm.	RIBOFLAVIN	2.0 mg.
CALCIUM	1.12 Gm.	NIACIN	6.8 mg.
PHOSPHORUS	0.94 Gm.	VITAMIN C	30.0 mg.
IRON	12 mg.	VITAMIN D	417 I.U.
COPPER	0.5 mg.	CALORIES	676

*Based on average reported values for milk.

Two kinds, Plain and Chocolate Flavored. Serving for serving, they are virtually identical in nutritional content.

rational therapy

through Specific Action in Diarrhea and Infectious Enteritis

Paoguan presents sulfaguanidine, colloidal kaolin, and pectin for prompt action in many forms of infectious diarrhea, colitis, and gastroenteritis. Produces rapid relief of the diarrhea and associated abdominal discomfort.

Antibacterial The antibacterial action of sulfaguanidine is largely confined to the intestinal tract. It is but slightly absorbed, hence is remarkably free of toxic systemic reactions. It is the sulfonamide of choice in many forms of infectious enteritis.

Demulcent Pectin performs the valuable function of combining with certain toxins and exerting a well-defined demulcent influence upon inflamed intestinal mucous membranes.

Adsorbent Both kaolin and pectin are highly adsorptive and aid in the removal of toxins and bacteria, reducing the severity of the invasion.

Paoguan is available through all pharmacies in gallon and pint bottles.

THE S. E. MASSENGILL COMPANY
Bristol, Tenn.-Va.
NEW YORK • SAN FRANCISCO • KANSAS CITY

SEMCO

Each 5 cc. of Paoguan contains:

Sulfaguanidine	0.5 Gm.
Colloidal kaolin	2 Gm.
Pectin	0.04 Gm.

Combined in a palatable vehicle containing aromatics and carminatives.

PAOGUAN

SULFAGUANIDINE • PECTIN • KAOLIN

Resistant
Bacterial Infections

AUREOMYCIN

HYDROCHLORIDE LEDERLE

Aureomycin is now widely used for the treatment of infections that have proven resistant to other chemotherapeutic agents, or combinations of such agents. Aureomycin does not commonly provoke resistance in bacteria, and its ability to penetrate cell membranes and diffuse through the body fluids assures the presence of the therapeutic material everywhere it is needed.

Aureomycin has been found effective for the control of the following infections: African tick-bite fever, acute amebiasis, bacterial and virus-like infections of the eye, bacteroides septicemia, boutonneuse fever, acute brucellosis, gonorrhea resistant to penicillin, Gram-positive infections (including those caused by streptococci, staphylococci, and pneumococci), Gram-negative infections (including those caused by the coli-aerogenes group), granuloma inguinale, *H. influenzae* infections, lymphogranuloma venereum, peritonitis, primary atypical pneumonia, psittacosis (parrot fever), Q fever, rickettsialpox, Rocky Mountain spotted fever, subacute bacterial endocarditis resistant to penicillin, tularemia and typhus.

LEDERLE LABORATORIES DIVISION
AMERICAN Cyanamid COMPANY
30 Rockefeller Plaza, New York 20, New York

AUREOMYCIN

Capsules: Bottles of 25, 50 mg. each capsule. Bottles of 16, 250 mg. each capsule.
Ophthalmic: Vials of 25 mg. with dropper; solution prepared by adding 5 cc. of distilled water.

A Major Advance in Peptic Ulcer Therapy:

Banthine*

BROMIDE

Brand of Methantheline Bromide

AN ORIGINAL RESEARCH PRODUCT PROVIDING A NEW THERAPEUTIC APPROACH

ENCOURAGING results with Banthine in a group of refractory peptic ulcer patients were reported by Longino, Grimson, Chittum and Metcalf[1] and later in an enlarged series of patients by Grimson and Lyons[2]. Their observations interested other investigators[3-5] who have obtained equally promising results with this new drug.

These early observers[1,2] noticed that symptoms are sometimes relieved as soon as fifteen minutes following the institution of therapy, and in patients with long-standing, intractable pain discomfort becomes mild and intermittent or disappears. Their conclusions regarding healing of the ulcer are based on roentgenographic evidence.

Thorough pharmacologic investigations indicate that Banthine is a potent but safe drug in therapeutic doses. In these studies no abnormality of the blood or urine or other evidence of toxicity was observed.

BANTHINE: THE DRUG

Chemically, Banthine is β-diethylaminoethyl xanthene-9-carboxylate methobromide. Its generic name is methantheline bromide. It should be noted that the xanthene group bears no relation to the more familiar xanthine group of drugs.

A True Anticholinergic

Banthine may be described as a true anticholinergic drug. In therapeutic doses it controls autonomic stimuli which result in the vagotonia characteristic of the ulcer diathesis. This action is effected at

*Trademark of G. D. Searle & Co.

the ganglions of both the sympathetic and parasympathetic systems and, in addition, at the postganglionic nerve endings of the parasympathetic system alone. Thus, the resulting therapeutic action is that of control of excessive parasympathetic stimuli effecting a consistent reduction of gastric hypermotility and, in most patients, a reduction in the hyperacidity which is commonly associated with peptic ulcer.

ADMINISTRATION

Because of the prominence of emotional or situational stresses in the ulcer patient and because these stresses vary in each patient, it is necessary to adjust Banthine dosage to meet individual requirements. Initial dosage may be 50 or 100 mg. (one or two tablets) every six hours, day and night, with subsequent adjustment to the patient's needs and tolerance. In addition, the usual adjunctive measures of diet, rest and relaxation should be prescribed for at least the first few weeks of treatment.

It is important that the usual high night secretions be controlled. To this end it is recommended that the night dose be taken six hours prior to the usual time of arising. Further, after the ulcer is healed, it is important that the patient be placed on a maintenance dosage schedule if he is to have a reasonable assurance of nonrecurrence. The maintenance dosage may well be approximately one-half the therapeutic dose and no evidence of chronic toxicity has been observed in maintenance dosage although this experience covers only a period of sixteen months.

Patients may report dryness of the mouth, mild degrees of blurring of vision, slight difficulty of urination or gastric fulness; these symptoms usually decrease or disappear on continued medication but if they are severe they may require dosage adjustment. Untoward reactions with Banthine therapy have not been encountered.

More complete suggestions for Banthine administration are available to the medical profession in Searle Reference Manual No. 40.

Banthine is a product of Searle research. G. D. Searle & Co., Chicago 80, Illinois.

REFERENCES

1. Longino, F. H.; Grimson, K. S.; Chittum, J. R., and Metcalf, B. H.: An Orally Effective Quaternary Amine, Banthine, Capable of Reducing Gastric Motility and Secretions, Gastroenterology 14:301 (Feb.) 1950.
2. Grimson, K. S., and Lyons, C. K.: Scientific Exhibit at the American Academy of General Practice, St. Louis, Feb. 20-23, 1950.
3. Grollman, A.: Pharmacology and Therapeutics, ed. 14, Philadelphia, Lea & Febiger, in press.
4. Dragstedt, L. R.: Personal communication, March 23, 1950.
5. Collins, E. N.: Personal communication, March 28, 1950.

Oral therapy for allergic rhinitis

Side effects "much fewer and much less severe"[1]*

In a recent clinical study comparing antihistaminics at various dosage levels, Neohetramine proved to be highly effective therapeutically and exceptionally well-tolerated.[1]

NEOHETRAMINE®

HYDROCHLORIDE

is an effective antihistaminic for the relief of catarrhal symptoms and dermatosis due to allergy.

[1]Schwartz, E.: Ann. Allergy 7:770 (Nov.-Dec.) 1949.

*From "Diseases of the Skin," by O. Ormsby and H. Montgomery, courtesy of Lea & Febiger, Phila., Pa., 1945.

TABLETS
25 mg. Packet of 12, vial of 25, bottles of 100 and 1000
50 mg. Bottles of 100 and 1000
100 mg. Bottles of 100 and 1000

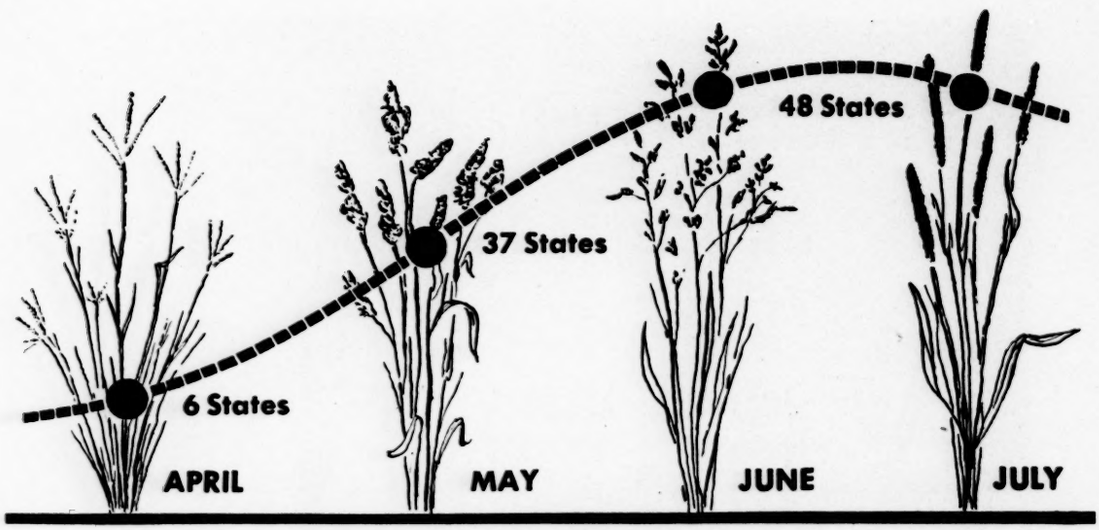
SYRUP
6.25 mg. per cc.
Pints and gallons

CREAM
Contains 2% Neohetramine
Tubes of 1 oz.

Neohetramine is the registered trademark of the Nepera Chemical Co., Inc., for its brand of thonzylamine—N, N-dimethyl-N' p-methoxybenzyl-N' (2-pyrimidyl) ethylenediamine.

Wyeth Incorporated • Philadelphia 3, Pa. Wyeth®

MEDICONE COMPANY • 225 VARICK STREET • NEW YORK 14, N.Y.



This graph shows the number of States where hay fever, due to grass, prevails during the Spring and early Summer months.

Dreaded Season...

Many hay fever sufferers now are entering what is ordinarily their most uncomfortable season. Fortunately, more and more patients each year are enjoying the therapeutic benefits of Neo-Antergan® Maleate. Because of its safe and, in many cases, strikingly effective action in relieving the distressing symptoms of allergy—Neo-Antergan has become a favorite antihistaminic with physicians and patients.

Neo-Antergan is advertised exclusively to the medical profession. Your patients can secure its benefits *only through your prescription.*

Complete information concerning Neo-Antergan Maleate and its clinical uses will be sent on request.

MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY

Neo-Antergan®

MALEATE

(Brand of Pyranisamine Maleate)

(N-*p*-methoxybenzyl-N′, N′-dimethyl-N-*a*-pyridylethylenediamine maleate)

COUNCIL ACCEPTED

what makes Donnatal so effective... so safe?...

BELLADONNA ALKALOIDS

...BALANCED WITH

LABORATORY PRECISION

Donnatal—one of the most widely employed spasmolytics today—derives its ever-increasing professional popularity from its dependable efficacy and its safety...demonstrated by controlled investigative studies,[2,3,4,5,6] and by gratifying clinical results in daily practice.

The secret of its success lies in its employment of only *natural belladonna alkaloids*,[1,2,4] in precisely and optimally balanced ratios—together with a small content of phenobarbital, for relief of the psychogenic factor by central and peripheral nervous sedation.

A. H. ROBINS CO., INC. • RICHMOND 20, VA.

Ethical Pharmaceuticals of Merit since 1878

[redacted] Hypertonicity, hypermotility and spasm of smooth muscle of the gastrointestinal, biliary and genito-urinary tracts. Donnatal is often effective in angina pectoris, hypertension, hyperacidity, parkinsonism and motion sickness.

[redacted] ***Tablets or Capsules:*** 1 to 2, three or more times daily (up to 9 tablets or capsules may be given within 24 hours without toxic effects).

Elixir: Infants: ½ teaspoonful 2 or 3 times daily, as necessary. Children: 1 teaspoonful, 2 or 3 times daily, as needed. Adults: 1 or 2 teaspoonfuls, 3 or 4 times daily.

[redacted] 1. Goodman, L. and Gilman, A.: The Pharmacologic Basis of Therapeutics, The Macmillan Co., New York, 1941. 2. Kilstein, R. I.: Rev. Gastroenterol., 14:171, 1947. 3. Lee, L. W.: Nebraska State Med. J., 34:59, 1949. 4. Morrissey, J. H.: J. Urol., 57:635, 1947. 5. Ricci, J. V.: Contributions from Dept. of Gynecology, City Hospital, New York, 1946, New York Medical College, New York, 1947. 6. Stephens, G. K.: J. Oklahoma St. Med. Assoc., 42:246, 1949.

℞

Robins

Terramycin

Effective against a wide spectrum of bacterial, viral, rickettsial agents, and certain important protozoan organisms.

Terramycin

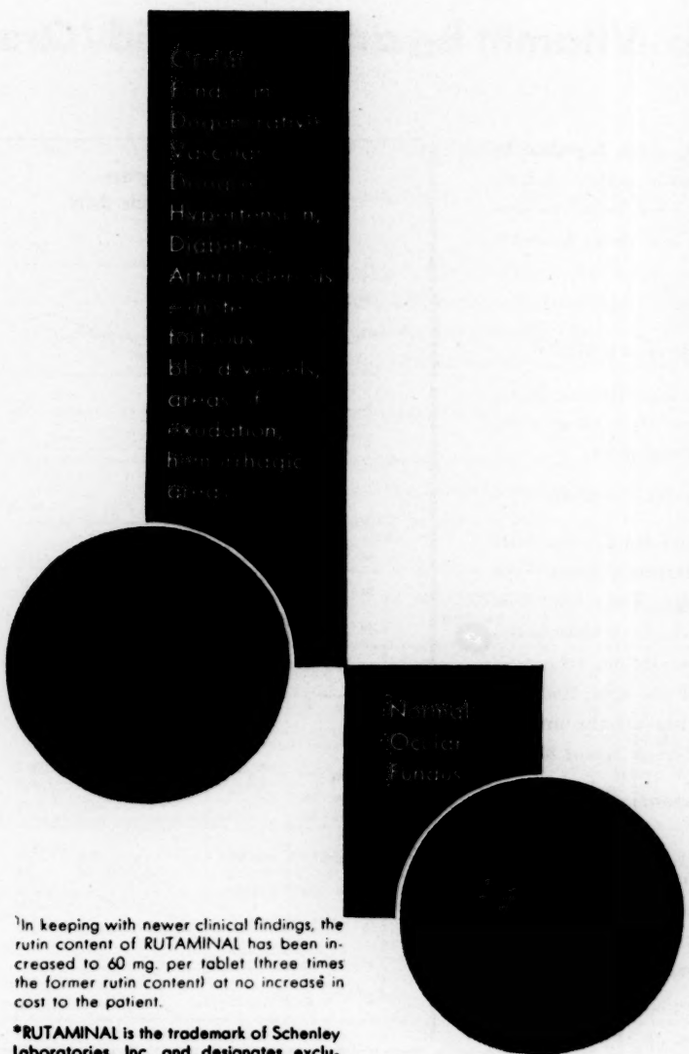
is available in 250 mg. capsules. 16 to the bottle. Dosage range—depending on the infection being treated—is from 2 to 3 grams daily in divided dosage.

indicated for: *acute pneumococcal infections, including lobar pneumonia, bacteremia; acute streptococcal infections, including erysipelas, septic sore throat, tonsillitis; acute staphylococcal infections; bacillary infections, including anthrax; urinary tract infections due to E. coli, A. aerogenes, Staphylococcus albus or aureus and other Terramycin-sensitive organisms; brucellosis (abortus, melitensis, suis); hemophilus infections, including whooping cough (exclusive of meningitis); acute gonococcal infections; syphilis; lymphogranuloma venereum; granuloma inguinale; primary atypical pneumonia; herpes zoster; typhus (scrub, epidemic, murine); rickettsialpox; amebiasis (Endamoeba histolytica).*

Pfizer

CHAS. PFIZER & CO., INC.
Brooklyn 6, New York

RUTAMINAL*



the
protection
of
rutin [1]
the
action
of
aminophylline
the
sedation
of
phenobarbital
—for
use
in
selected
cardiovascular
and
diabetic
conditions
in
which
excessive
capillary
fragility
presents
a
complicating
hazard
—bottles
of
100
tablets

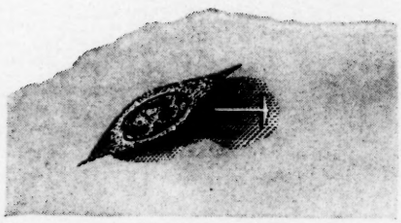
[1] In keeping with newer clinical findings, the rutin content of RUTAMINAL has been increased to 60 mg. per tablet (three times the former rutin content) at no increase in cost to the patient.

*RUTAMINAL is the trademark of Schenley Laboratories, Inc. and designates exclusively its brand of tablets containing rutin, aminophylline, and phenobarbital.

schenley laboratories, inc., **350 fifth ave., new york 1, n. y.**

© Schenley Laboratories, Inc.

April 15, 1950



THE STATUS OF B_{12} ANTI-ANEMIA THERAPY:

Vitamin B_{12} and Folic Acid (Oral)

VITAMIN B_{12} AND FOLIC ACID, given together by mouth, have a pronounced synergistic action. A non-therapeutic amount of folic acid has been found to promote the utilization of vitamin B_{12} in oral doses formerly believed to be ineffective.

HOW DOES IT ACT?

Vitamin B_{12} for extrinsic factor-like activity

Given by mouth, vitamin B_{12} acts like the extrinsic factor of food. The effective oral dose is some 30 to 60 or more times greater than the effective parenteral dose.

Folic acid for intrinsic factor-like activity

Meyer and associates[1] assert that, in vitamin B_{12} and folic acid therapy, "folic acid acts like 'intrinsic factor'" in that it promotes utilization of vitamin B_{12}. The role of folic acid "on the release, absorption or synthesis of vitamin B_{12} in the intestinal tract" is open to speculation, according to Cartwright, Wintrobe and others.[2] Folic acid, Best and Taylor[3] state, may possibly "act to stimulate the production of the intrinsic factor or be the intrinsic factor itself."

B_{12} and folic acid are essential

Luhby and Wheeler[4] suggest:

1. If a folic acid deficiency is profound, even large doses of vitamin B_{12} are hematologically inert.
2. If a severe vitamin B_{12} deficiency exists, large doses of folic acid should be hematologically inactive.

They advance the following possible equation:

(Folic acid) x (Vitamin B_{12}) ⟶ (E.M.F.)

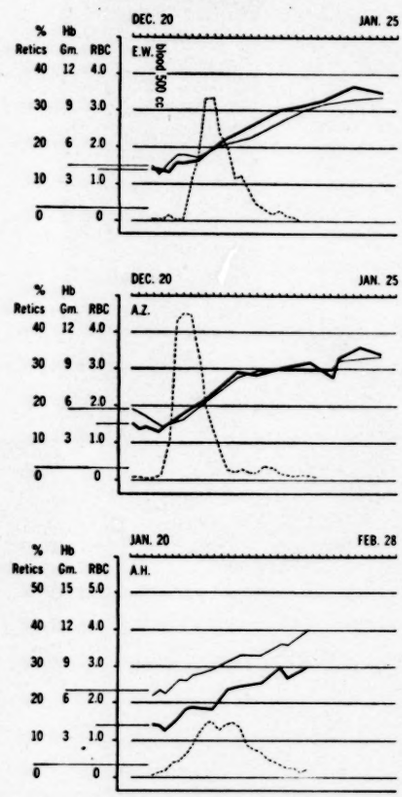
WHAT ARE THE RESULTS OF THERAPY?

With vitamin B_{12} and folic acid, given orally, hematologic response frequently parallels that of parenteral vitamin B_{12} therapy. Ordinarily, clinical remission is both prompt and dramatic. Furthermore, in patients so far studied, oral vitamin B_{12} and folic acid apparently protects against and reverses manifestations of combined system disease.

HOW IS IT AVAILABLE?

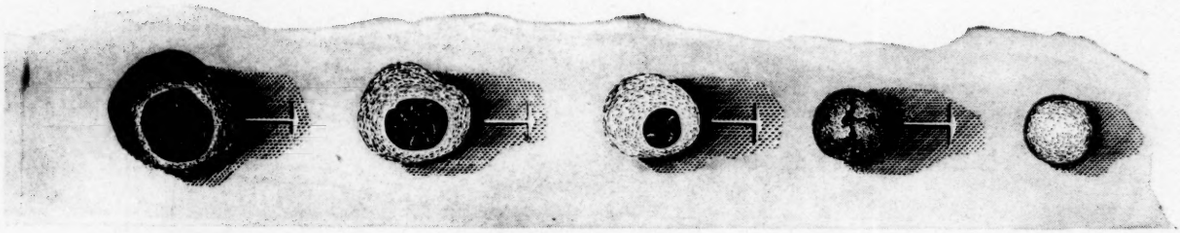
Supplied as RUBRAFOLIN *(See next page)*

Hematologic response to 1 Rubrafolin Capsule daily



INDICATIONS FOR B_{12} THERAPY

Macrocytic anemias ordinarily respond well to vitamin B_{12} therapy. These include pernicious anemia without neurologic involvement, pernicious anemia with combined system disease, nutritional macrocytic anemia, tropical sprue, non-tropical sprue. (Pernicious anemia of pregnancy responds best to folic acid therapy.)



and Vitamin B_{12} Alone (Parenteral and Oral)

Vitamin B_{12} alone—parenteral administration

In most anemias characterized by megaloblastic arrest of the bone marrow vitamin B_{12} will:

1. Reverse megaloblastic arrest of the bone marrow.
2. Protect against and reverse neurologic changes.
3. Reverse gastrointestinal manifestations.
4. Produce rapid, marked and—in most cases—sustained clinical improvement.

Vitamin B_{12} alone—oral administration

When given alone by mouth, vitamin B_{12} is not as hematopoietically active as it is when it is injected. In the megaloblastic anemias, vitamin B_{12} is not easily absorbed by the gut. Much larger doses are necessary if a therapeutic effect is to be obtained.

	THERAPEUTIC DOSAGE	MAINTENANCE DOSAGE	REMARKS	SUPPLY
RUBRAFOLIN* (25 micrograms of vitamin B_{12}, 1.67 mg. of folic acid per Capsule).	1 Capsule daily	1 Capsule daily.	If response is submaximal at the end of 10 days or 2 weeks, double the dose. In case response is not optimal by the fourth week, the patient should be placed on parenteral Rubramin.	Bottles of 100 Capsules.
RUBRAMIN* Capsules (25 micrograms of vitamin B_{12} per Capsule).	6 to 12 Capsules daily.	To be adjusted to patient's needs.		Bottles of 100 Capsules.
RUBRAMIN 15 or 30 microgram ampuls; 5 and 10cc. vials—30 micrograms per cc.	15 to 30 micrograms once or twice a week.	15 micrograms every 2 weeks or 30 micrograms once a month.	Larger therapeutic doses must be used in the presence of moderate to severe neurologic involvement.	1 cc. ampuls, 15 or 30 micrograms of vitamin B_{12} per ampul. Boxes of 5. 5 and 10cc. vials, 30 micrograms of vitamin B_{12} per cc. also available: Solution Rubramin Crystalline (Squibb Crystalline Vitamin B_{12} Solution) in 1 cc. ampuls, containing 15 micrograms of crystalline vitamin B_{12}.

Bibliography: 1. Meyer and associates: A. J. Clin. Path. (in press). 2. Cartwright, Wintrobe and associates: Blood 4:301, 1949. 3. Best and Taylor: The Physiological Basis of Medical Practice, ed. 5, Baltimore, Williams & Wilkins, 1950, p. 87. 4. Luhby, A. L.; and Wheeler, W. E.: The Health Center Jl. (Ohio State Univ.) 3:1, 1949.

*Patients to receive Rubrafolin or Rubramin Capsules should be individually selected. The physician should rule out patients with severe gastrointestinal disturbances, severe cardiac failure or severe anemia when pernicious anemia is present. Patients such as these—and those with severe neurologic involvement—respond better to parenteral Rubramin therapy. Neurologic changes should be watched for closely. At the first sign of new neurologic involvement, the patient should be placed on parenteral Rubramin therapy.

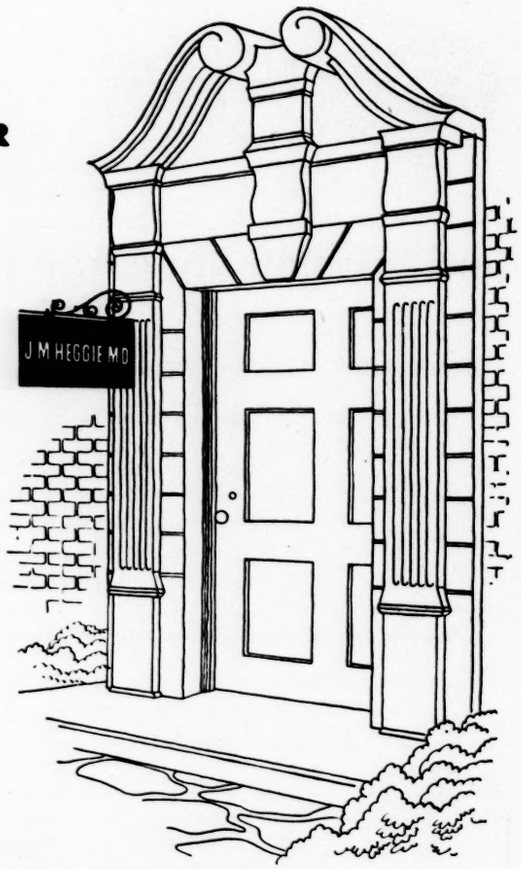
'RUBRAMIN' AND 'RUBRAFOLIN' ARE TRADEMARKS OF E. R. SQUIBB & SONS

Rubramin
SQUIBB VITAMIN B_{12} CONCENTRATE

Rubrafolin
SQUIBB VITAMIN B_{12} CONCENTRATE AND FOLIC ACID

SQUIBB

BEHIND THIS DOOR



. . . is the man who merits the confidence of millions of married women seeking advice about contraception. For the doctor this is a grave responsibility. The finality of pregnancy brooks no hit or miss preventive measures. When childbearing is contraindicated, only an effective means of contraception can be considered. This explains the widespread professional acceptance of Lanteen contraceptive products.

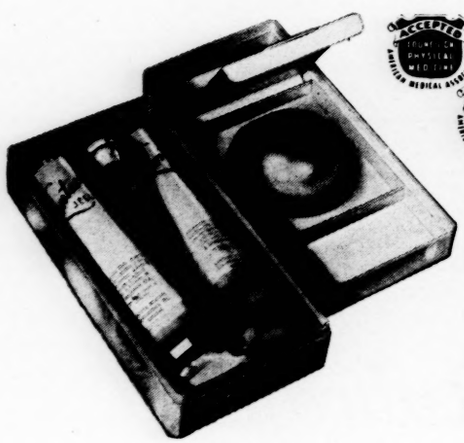
The diaphragm and jelly method of contraception, which comprises the Lanteen Technique, is accepted by leading authorities as one of the safest and most effective means of preventing conception. The Lanteen Diaphragm, made of the finest rubber and watch spring steel, is scientifically designed for complete comfort and dependable protection. Lanteen Jelly, containing hexylresorcinol, has been proven spermatocidal in the shortest time interval recorded in the officially recognized Becker and Gamble[1] test. Despite this potent sperm-destroying action, the jelly is actually soothing to sensitive membranes.

Both the Lanteen Diaphragm and Lanteen Jelly are accepted by the Council on Physical Medicine and the Council on Pharmacy and Chemistry of the American Medical Association, respectively.

Lanteen Jelly contains: Ricinoleic Acid, 0.50%; Hexylresorcinol, 0.10%; Chlorothymol, 0.0077%; Sodium Benzoate and Glycerine in a Tragacanth base.

1 Becker, B., and Gamble, C J.: The Spermicidal Times of Contraceptive Jellies and Creams, Human Fertility, *11*:111 (Dec.) 1946.

Write for literature describing the Lanteen Method of Contraception.



The Lanteen Diaphragm and Lanteen Jelly are accepted by the Council on Physical Medicine and the Council on Pharmacy and Chemistry of the American Medical Association, respectively.

Lanteen

MEDICAL LABORATORIES, INC.

2020 Greenwood Street

Evanston, Illinois

the best of Protein

and

B

Complex

Vitamins!

Here is an exceptionally pleasant-tasting new dietary supplement for management of anorexia, febrile illnesses, convalescence, malnutrition, pregnancy and lactation.
The formula tells the story:

Each 45 cc. (3 tablespoonfuls) of TRONIC® provides:

Protein hydrolysate (45% amino acids)	6.8 Gm.	Calcium Glycerophosphate	130 mg.
Thiamine hydrochloride	4 mg.	Sodium Glycerophosphate	260 mg.
Riboflavin	2 mg.	Manganese Glycerophosphate	24 mg.
Pyridoxine hydrochloride	1 mg.	Potassium Glycerophosphate	16 mg.
Niacinamide	30 mg.	Alcohol	17%

with flavoring agents added

Tronic®

Compound

SHARP & DOHME

TRONIC Compound is an unusually complete, well formulated nutritional supplement, and will be found particularly useful for geriatric and pediatric patients, as well as in other branches of medicine. Supplied in *Spasaver*® pints and gallon bottles.
Sharp & Dohme, Philadelphia 1, Pa.

DISTINCTLY DIFFERENT

the inside story

In appearance these two tablets are the same, yet their enteric coatings differ widely in principle and reliability.

Release of medication in the intestines is uncertain with coatings which depend on gastric acidity for remaining intact and on an alkaline environment for dissolving. These conditions are variable. They are especially altered in old age, in certain diseases, and following the use of many drugs.

Reliable release in the intestines is achieved with 'Enseals' (Timed Disintegrating Tablets, Lilly). The continuous moisture of the alimentary tract ruptures their hydrophilic coating after an appropriate interval; hence, 'Enseals' rely upon a constant condition of physiology and the inevitable passage of time.

SPECIFY
ENSEALS

to avoid gastric distress from sodium salicylate or other irritating chemicals

to delay the effect for nocturnal control with such drugs as 'Histadyl' (Thenylpyramine, Lilly)

to smoothen effect through gradual release of such potent agents as diethylstilbestrol

ELI LILLY AND COMPANY • INDIANAPOLIS 6 INDIANA, U.S.A.

Complete literature on 'Enseals' is available from your Lilly medical service representative or will be forwarded upon request.

The American Journal of Medicine

VOL. VIII JUNE, 1950 NO. 6

Editorial

The Clinical Laboratory and Training for Internal Medicine

DEVELOPMENT of internal medicine in recent years shows a strong tendency to disrupt a relationship between the internist and the clinical laboratory which grew up during the time of richest development of diagnostic methodology. During this time the relationship between internists, especially young physicians in training, and the clinical laboratory was most intimate and rewarding. Internists frequently took the lead in the development of clinical laboratory methods, and the daily use of what today would be called simple, crude laboratory procedures played a large part in the training of the young physician. In many places there is a tendency to deprive the young physician in training of the possibilities for learning the usefulness of laboratory procedures in the study of his patients. Such changes have come about not because of lessened emphasis upon the role of the laboratory but in association with increased use of and dependence upon laboratory procedures. It may well be fair to say that there are young men in training for internal medicine who are coming to visualize laboratory examination solely in terms of a written report returned from a central laboratory which they rarely if ever visit. This unhealthy trend may be traced to the great increase in the use of the laboratory in what is called "complete examination" and the centralization of clinical laboratory work. Other important influences are the disfavor into which the roughly quantitative methods have fallen as compared with the more accurate procedures used in clinical investigation in our University Hospitals. In this movement government hospitals, notably those of the military services and the Veterans Administration, have had a large influence in establishing the practice that practically all laboratory procedures, including the simplest sort, be done in a central laboratory so that in many hospitals students, interns and residents make little or no use of the simple ward laboratory. In some hospitals the practice of direct examination of smears of exudate, sputum and blood by the physician closest to the patient has fallen into complete disuse. In the best teaching hospitals residents and research fellows pursuing their graduate training in medicine are sometimes so preoccupied with the exceedingly complex procedures of clinical research as to neglect the use of simpler procedures which formerly were a standard part of the training of the internist.

One of the consequences of these developments is a sense of insecurity by many physicians unless a multitude of the laboratory procedures are at their disposal. However, increase in budgets for central clinical laboratories for many large hospitals has not been adequate to keep pace with the increasing demand for multiple and ex-

pensive procedures so that the character of the work done is sometimes inferior. Physicians then may have available a great number of methods but carried out so badly as to have little meaning. The physician thinks he must refuse to accept a result unless it agrees with his otherwise derived concept of the patient's diagnosis and thereby may lose his very best lead to an unusual or unexpected diagnosis. Workers in central laboratories may likewise become cynical about the intelligence shown by the clinician in requesting obviously needless procedures, resent the extraordinarily large volume of work they are called upon to do and turn their attention to completing the day of drudgery rather than to devoting themselves to intelligent collaboration in solving problems in sick people. Laboratory procedures which may offer guidance in grave emergencies, particularly when needed on holidays or at night, may be done so poorly as to be confusing rather than helpful.

The following suggestions seem appropriate: Much of clinical laboratory examination ought to be performed by those most directly interested and responsible for the individual patient. The simple laboratory adjacent to the ward should be continued or revised and expanded. Greater use should be made of qualitative or only roughly quantitative methods, and efforts should be made to develop more satisfactory methods in this category of simple procedures. Elaborate, expensive methods should be reserved for the carefully thought out and planned attack. Those in a supervisory capacity might compliment their juniors for their discrimination in limiting the number of laboratory procedures employed rather than conducting a systematic campaign to compel the use of many valueless procedures. When both approximate and accurate, but expensive and difficult, methods for the same purpose are available, the two kinds might be used in parallel in the study of individual patients in order to demonstrate the usefulness and limitations of both sorts of procedure. As a teaching exercise one physician might have available only the results of simpler tests while another has access to the results of strictly quantitative methods with the idea of finding out whether significant differences in diagnosis or management would result.

As valuable as an elaborate system may be, there are rich opportunities for the individual physician guided only by his own observations to go quickly to the heart of a matter of diagnosis or control of therapy. Utilization of these opportunities can have the greatest practical value for patients and may confer spiritual rewards upon the physician.

ROY H. TURNER, M.D.

Clinical Studies

Symptom Patterns of the Hyperventilation Syndrome*

RAYMOND L. RICE, M.D.
Milwaukee, Wisconsin

WHILE the hyperventilation syndrome has been known for many years,[1–3] its threshold of recognition remains high. Medical students as well as practitioners frequently state that they have never heard of this condition. Several factors are responsible for the unfamiliarity of the profession with this syndrome. Standard medical texts do not mention the hyperventilation syndrome as such. Monographs on cardiovascular disease each devote only a very few paragraphs to this condition. Articles relative to the hyperventilation syndrome appear only occasionally in the literature, for the most part in the specialty journals. It is not unusual, therefore, that the patient with this syndrome is often unrecognized by the practitioner to whom he goes for advice and treatment.

The treatment of functional disorders occupies a prominent place in the average physician's daily routine. When 1,000 consecutive office charts were investigated with the view of finding the frequency of patients who complain of signs and symptoms directly or indirectly attributable to the hyperventilation syndrome, 107 records were obtained in which one of the major diagnoses was hyperventilation syndrome, an incidence of 10.7 per cent. Although the incidence seems high, McKell[4] has reported an incidence of 5.8 per cent in 500 consecutive patients with gastrointestinal complaints. Such a large segment of the medical practice bears critical evaluation.

MATERIAL FOR STUDY

Material for this study was obtained from the charts of 1,000 consecutive patients seen in the author's office practice during the years 1943 through 1946. The following minimum procedures were performed on each patient, namely, complete history and physical examination including rectal and vaginal, roentgen examination of the chest, electrocardiogram, complete blood count and differential, gross and microscopic urinalysis, sedimentation rate, basal metabolic rate and the Kahn test. Other diagnostic procedures were performed when necessary.

The patients in this series represented the average subject presenting himself to an internist for examination.

SYMPTOMATOLOGY

The symptoms of hyperventilation have been described to include "numbness and tingling of the hands, feet, and face; buzzing in the head; varying degrees of reduction in the level of consciousness, described as dizziness, lightheadedness, giddiness, or fainting; blurring of vision; dryness of the mouth; stiffness of the muscles and tetany."[5] The symptomatology will be presented as it was described by the 107 patients under study. No attempt will be made to cite percentages; rather, the broad symptom patterns will be portrayed as they actually occurred.

Breathlessness. Symptom recitals by the hyperventilators under investigation re-

* From the Department of Medicine, Mount Sinai Hospital and Marquette University School of Medicine, Milwaukee, Wis.

vealed several distinct types of breathlessness. Similar variances in breathing patterns have been noted by other authors.[1,6]

The first form occurred as an explosive reaction associated with terror, pain or other emotional upsets. It served the purpose of "preparation for fight or flight," permitting prolonged physical exertion or even breathholding.[5] A typical example was the female patient who while sleeping fitfully, half awake yet half asleep but still able to feel the terrifying flip-flop of her heart maneuvering through a premature ventricular systole, sat up in bed and gasped with fright.

A deep gasp without a purpose to justify or sustain it makes for a sensation of smothering in these patients. Other gasps follow and the train of symptoms mentioned previously may ensue. If the reduction in the level of consciousness is great, other neurotic patterns may manifest themselves, namely, weeping, increased anxiety and more profound hysterical states. This climactic explosive gasp or deep breath is a normal expression of anxiety and may occur in perfectly normal individuals under stress.

The second and most common type of breathing pattern in the hyperventilation syndrome as evinced in this series was the deep breath or sigh the patient took to relieve himself of emotional tension. This sigh was usually not crisis-like or explosive but occurred in cycles during the day or night. It often gave rise to crisis-like episodes because of the frightening symptoms it occasionally produced but it usually began as a benign, tension-relieving, neurotic habit.

Detailed histories of the breathing phenomena of these patients revealed several attributes common to both of the aforementioned types of breathlessness. They both occurred at rest. Most climactic attacks, particularly the smothering spells, took place at night just before the patient fell asleep or immediately on awakening. They occurred before but not during great physical or mental activity (preparation for battle, protection, etc.).

Most attacks of the cyclic, episodic or second type occurred at *rest* or *after* physical exertion. While Wood[6] pointed out that hyperventilation occurs at rest, the patient's complaints on first examination would seem to belie this. "I get tired and short of breath when I wash" or "I get short of breath and dizzy when I rake the lawn" usually resolved itself into the following. When actually raking the patient was not conscious of breathlessness. When he stopped handling the rake and paused for rest, leaning on the rake for support, a deep, sigh-like breath escaped him which in turn was followed by another deep, sigh-like breath. The patient who complained of shortness of breath while climbing the stairs usually admitted that his breathing was of a sighing type and occurred after he stopped to rest from the exertion of climbing.

No cases of sighing-like respiration occurred in this group while the subject was moderately active, either physically or mentally. All of the patients experienced the episodes while daydreaming or performing routine jobs such as wiping the dishes, shopping, playing bridge, occupations which required little physical or mental activity or were associated with long periods of automatic action. Many of these patients traced their first attack of this phenomenon to a hospital stay when they either received an anesthetic and could remember coughing or choking or were instructed in deep-breathing exercises or both; to an emotional upset accompanied by a great deal of crying or laughing; to a period of yawning induced by excessive physical or mental fatigue; to sudden fright induced by environmental situation or during a quiet rest when some normal body mechanism gave rise to an unusual symptom and caused fright and gasping. Thus many patients recited that they first noted breathlessness following recovery from pneumonia or after a cesarean section. One patient was frightened out of her sleep by her husband who was having a convulsion. Many stated that their symptoms began

with an unusual flutter or churning in their chest (transient arrhythmia).

Overbreathing has been described as a habit[7] and consideration of the syndrome in this light may serve a useful purpose. Having legitimately taken a long or deep breath in response to a physiologic or psychologic need because of fright or relief from tension, these patients continue to breathe deeply because they have developed the habit of overbreathing when thrown into an unhappy situation. Whereas one individual under tension might reach for a cigarette or a piece of chocolate, these people begin to hyperventilate. In the choice between means for relief of tension or preparation for battle, real or imaginary, these patients prefer to sigh it out.

Hyperventilation can be performed in many ways. Patients were observed to be sighing, yawning or sniffing. They indulged in hacking or clearing of the throat or heaving of their chests, little tics, each a form of overbreathing. Many patients converted from one type of hyperventilation to another while undergoing therapy for the condition.

While some subjects were aware of sighing and yawning and listed it or breathlessness as the chief complaint, many were not. Most patients hyperventilated while they gave their history. They excused their sighing or yawning by saying that "I can't get enough air," "When I take a breath, it doesn't do me any good," "My wind won't go all the way down" or "I feel as though I am going to choke for lack of air." Other patients in this series denied sighing or yawning only to be sharply contradicted by their spouses who accompanied them to the office and had noticed these symptoms on many occasions. Stead[8] has noted similar instances of unawareness of hyperventilation in affected subjects.

Pain in the Chest. Chest pain is a common symptom associated with functional cardiovascular disease and the hyperventilation syndrome. It does not necessarily occur while the patient is hyperventilating. Classification of complaints referable to chest pain by the hyperventilators in this group displayed the following forms and detailed characteristics, namely, (1) a sharp, fleeting, knife-like pain, usually exaggerated by breathing or bending, which starts in the left precordium or hypochondrium and radiates into the neck or back; (2) a dull, aching discomfort, usually over the precordium, lasting for minutes to hours and (3) a heavy, pressing sensation underneath the sternum accompanying the actual hyperventilation.

The first type frequently served as a trigger mechanism for an episode of hyperventilation. It usually disappeared before the attack was over, lasting only seconds. This sharp, knife-like pain exaggerated by respiration has occurred frequently in this study and, in the opinion of the author, was usually produced by an overdistended stomach pressing on the diaphragm. The pain could often be reduplicated by exerting pressure over the distended stomach. As will be pointed out later a great number of hyperventilators became aerophagic and a huge gas bubble was often demonstrated in the stomach of these patients.

A different explanation has been offered by Friedman[9] who took electrocardiograms at the onset of precordial pain and was able to note transient arrhythmia with the onset of pain in some patients and forceful, rapid heart action in others. He considered that the cause of the sharp, "excruciatingly severe, precordial pain was of intrinsic cardiac origin." He believed that in patients with functional cardiac disorders, arrhythmia or excessively forceful cardiac contractions caused actual pain which apparently stemmed from the nerve fibers in the cardiac musculature.

This subject bears further investigation. Many patients under study disclosed this type of pain. Most described their sharp pains as "cutting off my air." They held their chests in a position of exhalation until the pain disappeared and then noted the pain returning with a deep breath, much like pleuritic pain. Pressure over the distended stomach of susceptible patients

initiated both pain, tachycardia or premature ventricular systoles and an ensuing episode of hyperventilation.

The second type of pain of which patients complained was a dull ache, a persistent type of gnawing discomfort lasting hours which was usually present in the left anterior hemithorax and centered about the nipple. Patients also complained of local tender areas. Examination often disclosed muscle tenderness in areas of the anterior thorax and more frequently one or more exquisitely tender costochondral junctions.

Wood[6] and Friedman[10] pointed out that patients with this type of chest pain breathed in a peculiar fashion. Affected patients used only the upper chest musculature in breathing. Many subjects with functional cardiovascular disease but particularly those with the hyperventilation syndrome breathed in this manner. They were seen to heave their chests using the upper chest muscles and accessory muscles of respiration both in quiet respiration and in active hyperventilation. When asleep they reverted to abdominal breathing. These people suffered from diaphragmatic inertia. Even those individuals who used abdominal breathing while awake were found after the slightest physical exertion or emotional tension to change to upper chest breathing. Friedman[11] demonstrated that these patients' chest expansion was greatest in the upper third as distinct from the normal individual's greater expansion in the lower third of the thorax. He also observed fluoroscopically that the diaphragm remained relatively immobile during respiration.

He[12] further noted that the average respiratory pressure with severe functional cardiovascular disease was less than one-half that of normal individuals. The use of intercostal musculature alone rarely produced an expiratory pressure above 50 mm. of mercury. The diaphragm contracting against fixed intercostal musculature was the real factor in making a normal expiratory pressure, around 118 mm. of mercury. This factor, the force exerted by the contracting diaphragm, was absent in his hyperventilating patients.

An experiment by the same author[13] is pertinent to these observations. Patients were forced to breathe abdominally by strapping the upper portion of the chest down to the eighth rib in such a manner that upper chest breathing was strictly limited. The strapping was left on for six days. At the end of forty-eight hours the pain disappeared. When the tape was removed, the patients resorted to upper chest breathing again and the dull, precordial aching returned in twenty-four hours. When the reverse experiment was performed, when normal adults had the upper abdomen and lower chest immobilized with tape and were then forced to exercise, eight of ten experienced dull, precordial pain on the second day of the study. This sensation was due chiefly to excessive use of intercostal musculature in respiration because diaphragmatic action was limited by the adhesive bandages.

White[14] observed that the patient is made more aware of this discomfort by an active heart pounding against the "oversensitized thoracic wall." Thus it is left-sided pain that is most often experienced.

The immediate sense of heaviness and retrosternal pressure of which hyperventilating patients complain appears to be due primarily to fatigue plus exercise of chest musculature. A simple experiment in point is to contract the hand into a fist for five or ten consecutive times. An immediate sense of warmth, heaviness and fatigue occurs in the exercised hand. This same sensation probably occurs in the muscles and joints of the chest and contributes to the sense of smothering, fatigue and heaviness which the patient experiences at the onset of his overbreathing. Overbreathing is a fatiguing exercise and many patients complain bitterly of exhaustion and fatigue.

Symptoms Referable to the Nervous System. These include giddiness, numbness and tingling of the hands, feet and face, muscle tightening, lightheadedness, buzzing in the head, blurring of vision and syncope.

Giddiness occurred as a presenting symptom as often as did breathlessness in this survey. Most patients complained of dizziness but it was not dizziness or true vertigo which they experienced. None of the patients with uncomplicated hyperventilation noted the sensation of having his environment or himself turn or spin. Rather, he complained of a "floating feeling," "going under an anesthetic," a "sinking feeling" or a "blacking out." Numbness or tingling was a frequent concomitant of giddness and could readily be induced in susceptible patients by hyperventilating. In the usual case overbreathing caused giddiness first, then numbness and tingling and then (if it occurred) muscle tightening. Tetany, which will be discussed later, though much publicized was rarely seen with this syndrome. Syncope, which usually supervened if hyperventilation lasted long enough, terminated the increased ventilation and obviated tetany.

There is a mass of experimental evidence to account for giddiness which occurs as a result of hyperventilation. Davis and Davis[15] pointed out that definite electroencephalographic changes took place during hyperventilation. Engel, Ferris and Logan[5] observed a definite correlation between the slowing of the frequency of the electroencephalogram and the degree of reduction of awareness. Marked reduction in consciousness occurred when the EEG mean frequency was reduced to less than five cycles per second as compared with a normal of ten cycles per second.

Several factors influence the degree of slurring of the EEG and reduction in the level of consciousness.

1. The degree of slurring is greater in younger patients, greatest in children and young adults.[16]

2. The rate of hyperventilation: excessive pulmonary ventilation results in increased loss of carbon dioxide from the body. The usual concentration of CO_2 in the alveolar air of 40 mm. partial pressure of mercury may be reduced to one-half that value by overventilation.[17] This loss of CO_2 results eventually in a temporarily increased alkalinity of the blood. Among the many chemical changes which occur secondary to this temporary alkalinity are the following:

A. The effect on blood calcium: total blood calcium is unchanged but the available or ionized calcium may be temporarily lowered by the increased alkalinity present.

B. Respiratory alkalosis effects the release of oxygen from hemoglobin within the body. With low CO_2 tension in the blood, O_2 is given up reluctantly to the body tissues.[18] In sensitive tissues such as the brain the effects of anoxia become apparent. This alteration in the oxyhemoglobin disassociation curve results in anoxia and is mirrored by changes in the EEG.[19]

C. Tissues low in CO_2 pressure have been shown to evidence contraction of their vessels with resulting interference in tissue oxygenation because of altered circulation.[20]

Friedman[21] has demonstrated another factor dominant in causing cerebral anoxia and dizziness. On performing the Flack test in patients with functional cardiovascular disease who experienced dizziness with change of position (patient tries to sustain a column of 30 mm. of mercury for twenty seconds by blowing into a rubber tube connected to the bottom of the receptacle containing the mercury), a reduction in pulse pressure was noted in patients susceptible to giddiness. A rise in diastolic pressure with little change in systolic pressure was responsible for the reduced pulse pressure. He noted two other phenomena (1) the width and pulsatile excursions of the pulmonary artery conus and the cardiac contraction were decreased remarkably and (2) the patients were unable to perceive the end point of the calcium gluconate arm-to-tongue test in the normal time while he was performing the test. When it was not perceived at all, the end point was invariably noted within six seconds after the test was completed.

Friedman postulated that these patients with functional cardiovascular disease and giddiness suffered an intense pulmonic and systemic vasoconstriction in response to the

test which in turn effected "a retardation in the forward flow of blood as indicated by the inability of the giddy patients to detect calcium gluconate"; thus resulted cerebral anemia and dizziness.

Studies reveal[5] that the greatest reduction in CO_2 content and tension in the blood occurred in the first thirty to sixty seconds of vigorous hyperventilation. Single deep respirations lowered the carbon dioxide tension by 7 to 16 mm. After one minute continued vigorous hyperventilation lowered the CO_2 content only slightly over the initial levels obtained in the first minute. With different rates of hyperventilation the rate of fall of CO_2 varied but the eventual reduction was the same.

Thus can be explained the nervous system symptoms of either the explosive or cyclic breather. While the former notes his symptoms (giddiness) first, the latter eventually attains the same low degree of CO_2 content and thus develops similar symptoms.

3. Blood sugar levels: The degree of EEG slowing at relatively high blood sugar levels was slight (130 mg./100 cc.) while at lower blood sugar levels the slowing was marked. There was greater slowing of the EEG with low blood sugar and a greater reduction in consciousness. With high blood sugars the patient could hyperventilate for longer periods and tetany was more likely to develop.[22]

4. Oxygen tension of inspired air: Flack first noted that hyperventilation could be carried out more comfortably in atmospheres rich in oxygen. It has been pointed out[23] that marked slowing of the EEG occurred with inspiration of 10 per cent O_2 and 60 per cent nitrogen and little slowing was noted when patients inspired 100 per cent O_2.

5. Posture: Slowing of the EEG during hyperventilation was greater in the upright position than in the recumbent. This slowing was independent of any blood pressure fall during the upright position but was consistently accompanied by an increase in the pulse rate while the patient stood upright.[5]

Numbness in the hands, arms and face, and muscle stiffness occur following the onset of giddiness. They occur independent of EEG changes. They probably represent peripheral nerve rather than central or cortical involvement of the nervous system by anoxia.[5] The numbness and tingling may be due to sensory changes in the nerve, the muscle tightness and tetany to disturbances in the motor function of the involved nerves. Thus it may be that tetany arises from anoxia as well as alkalosis. Certain it is that no definite studies are reported as to the efficacy of calcium administration in overcoming tetany from hyperventilation.[24–26]

Syncope is one of the less frequent complications of hyperventilation. Fear of fainting and giddiness are common but actual syncope occurs rarely.

Several types of syncope were associated with the hyperventilation syndrome. (The outline is modified from Engel.[5])

A. Cerebral type: This is the purest type of syncope with hyperventilation. Here the level of consciousness is reduced to the point at which the patient cannot maintain himself erect and falls. It is accompanied by marked slowing in the EEG. It is relatively rare because the hyperventilation usually ceases reflexly before syncope occurs. Thus the patient thinks he is constantly on the verge of fainting.

B. Vasodepressor syncope: Here the anxiety accompanying hyperventilation may cause pallor, sweating, weakness and fall in blood pressure. It may occur during or after the episode.

C. Orthostatic hypotension: Hyperventilation will accelerate the fall in blood pressure in susceptible individuals with this condition.

D. Hysteria: This type of syncope is not associated with changes in skin color, pulse, blood pressure or EEG. It may be reduplicated by appropriate suggestions.

Gastrointestinal Symptoms. The gastrointestinal symptoms of the hyperventilation syndrome have been rarely referred to in the literature. As detailed by patients in

this survey they consist of dryness of the mouth, belching, abdominal bloating, gas pains and difficulty in swallowing.

Temporary dryness of the mouth may result from suppression of salivary secretion. This may occur as a reflex autonomic mechanism during emotion. Observation of the hyperventilating patient, however, leads one to suspect other, more important factors which are outlined later.

Most sighers swallow frequently. It is not unusual to note the hyperventilating patient first take his deep breath (or yawn, sniff or hacking cough), then moisten his lips with his tongue and swallow. This may occur as often as fifteen or twenty times during a period of five or six minutes.

During hyperventilation a column of air passes over the moist mucous membranes of the mouth and/or nose and pharynx. The passage of air makes for evaporation and loss of moisture from the surfaces of the naso- and oral pharynx. This evaporation is experienced by the patient as dryness in the nose, throat or mouth long before actual drying of these tissues occurs.

A simple experiment is to ask a normal subject to moisten his lips with his tongue and then allow his mouth to remain open. Within ten seconds subjects note dryness in their lips and mouth, and unless warned against it, will reapply their tongue to their obviously still moist lips.

To go one step further, a sense of dryness having developed in his mouth, the hyperventilator swallows to relieve himself of the sensation. Swallowing approximates the moist surfaces in his oral pharynx, remoistens them one against the other and temporarily relieves the patient of the sense of dryness. But evaporation and overbreathing continue, the sensation of dryness recurs and a vicious habit of swallowing is established.

Swallowing is not an innocuous habit. Each swallow introduces air into the stomach. It takes little time to accumulate large quantities of air which can be demonstrated in the gut by simple palpation and percussion or by demonstration of a magenblase under the left leaf of the diaphragm.

Aerophagia seemed to account for the belching and bloating described by the patients in this series.

A considerable number of patients in this study complained of difficulty in swallowing. The symptom resolved itself into several different forms. Some stated they felt a lump in the throat, others noted an inability to swallow effectively and some complained of choking on their food.

Best and Taylor state,[27] "If one wishes to swallow when the mouth is free of foreign material, a little saliva is passed backward by the tongue which serves as a mechanical stimulus for the initiation phases of the act. When the mouth is kept perfectly free of saliva, deglutition becomes impossible." Swallowing difficulties experienced by these patients seem plausible when their associated complaint of dryness of the mouth is considered. It seems reasonable to suppose that the complex muscular act involved in swallowing could, if carried on too rapidly, result in fatigue of the muscles performing the act. Both these factors, dryness of the mouth and fatigue, could account for the "choking," "feeling of a lump in the throat" or "difficulty in swallowing" which was described by these patients. Even when hyperventilation was controlled, this secondary symptom frequently persisted.

Increased salivation as an excuse for aerophagia is seen more rarely and probably is an over-response of the salivary secretory mechanism to the demand of the dry oral and pharyngeal tissues for lubrication.

Lesser Symptoms. Of the lesser symptoms noted in this syndrome palpitation deserves some comment. During the Flack experiment[28] when cardiac contractions were diminished in amplitude, the heart rate was increased. When cardiac size and contractions became normal, heart rate decreased.

Electrocardiographic changes have been observed during hyperventilation.[29] They consist of late inversion of T or S-T depression with marked lowering of T. Any or all leads may be involved.

Whether these changes are due to a relative alkalosis or result from the changes in the volume of the chest cage during hyperventilation is not known. Electrocardiographic changes have been noted in this study and approximate those described in the literature.

To breathlessness, chest pain, giddiness, syncope and gastrointestinal complaints must be added those symptoms common to all functional disorders. The patients in this series experienced fever (99.6° to 100.8°F.) sweating, headaches, muscle aches and pains, abdominal cramps, urinary frequency, flushes or chills, irritability, etc. Careful study was necessary to establish the diagnosis as functional and appropriate procedures were performed to rule out organic disease.

THERAPY

Before the syndrome can be treated it must be recognized. Careful questioning of each patient who complains of breathlessness, giddiness, numbness and tingling, pressure or pain in the chest will often give a clue as to the etiology of the condition. Voluntary hyperventilation will frequently but not always produce the symptoms in susceptible patients. It became obvious early in this study that simple recognition of the condition and reassurance of the patient would not relieve him of his symptoms, in spite of opinions supporting this view.[30]

These patients have developed a habit. They must be made to appreciate that they are sighing, sniffing, yawning or coughing. If they are not aware of these tics, they must be reminded by persons close about them each time they indulge in the habit. This forces awareness and awareness of overbreathing is the first step in overcoming the habit. Patients who sigh are instructed to watch for the appearance of the urge to take deep breaths. They are then told to suppress these breaths by taking, instead, a normal breath. Having done this they will have overcome the habit on one occasion. Being aware of this syndrome they will note a terrific urge to take another deep breath. Constant suppression by normal breathing during these episodes eventually breaks them of this habit.

At the inception of this study susceptible individuals were given a rational explanation of the syndrome and told to go home and forget about their condition. While the patient felt reassured in the office and was happy in the benign outcome of his interview, he frequently went home to experience a night of terror. Having taught the patient to observe the habit he now became acutely aware of the urge to indulge in it. The cyclic or episodic breather often became the explosive or climactic type.

To tell a man that he has a habit which is making him ill is one thing; to expect him to break himself of that habit without any mental or physical trauma is another. As a result of these experiences patients were told that they should expect to feel worse before they felt better. This explanation and the warning reassured the patient during the stormy hours of his abstinence from overbreathing. Patients were instructed to notify us of their condition from day to day. Failures were asked to return to the office for further instruction.

With few exceptions hyperventilators were able to overcome the habit within two or three days. Many successfully abolished this uncomfortable syndrome only to convert from one type of hyperventilation to another. Thus patients converted to sniffing, hacking, coughing, yawning, or stretching or heaving of their chests with recurrences of original uncomfortable side effects. Each conversion was treated as it arose and responded in about the same time as the original symptoms did.

Patients in this study have not been cured by rebreathing into a paper bag, by receiving injections of calcium, by breathing air rich in carbon dioxide or by holding their breath.[30] Suggestions of this nature overlook the fundamental physiologic processes involved in the production of this syndrome. It has been suggested that abdominal breathing be taught these pa-

tients.[30] Suppression of the urge to take a deep breath and substitution of normal breathing in its stead proved to be the only practical means of attaining this goal.

Once hyperventilation is overcome, psychotherapy may be instituted by those competent to administer it.

DIFFERENTIAL DIAGNOSIS

Although hyperventilation occurs with encephalopathies and drug poisoning, particularly with salicylates,[31] its origin in these disorders is relatively rare. The psychogenic hyperventilation syndrome must be considered whenever a patient complains of breathlessness, fatigue, giddiness, dizziness, chest pain, numbness and tingling, or syncope. Careful interrogation will usually reward one with enough information to rule the condition in or out. In healthy individuals, particularly, the history and complaints are so typical that the diagnosis is often apparent on presentation of the chief complaint.

"Angina pectoris, coronary disease, nervous breakdown, carotid sinus syndrome, epilepsy, hyperthyroidism and heart disease" were only a few of the labels attached to otherwise normal individuals in this study whose only disability was an aberration in the depth of their breathing.

More difficult is the separation of the symptoms of this syndrome from those symptoms arising out of organic disease. For while it is true that hyperventilation arises as a response to intense emotional experiences or as a vegetative neurotic symptom in healthy individuals, it likewise holds that the physically ill may suffer from the same syndrome in addition to their organic ills. Thus the fully digitalized compensated cardiac patient, who for no apparent reason becomes breathless, may have begun to hyperventilate. Evaluation of the symptoms is difficult. Venous pressure, vital capacity, breathholding tests, circulation times may offer little help in borderline cases of congestive failure. The breathholding test is particularly confusing as most normal hyperventilators have a diminished ability to perform this test.[32] Observation of the character of the breathing is perhaps the only criterion for diagnosis. In decompensated cardiac patients dyspnea, tachypnea and Cheyne-Stokes respiration develop but never a sighing type of respiration as a result of congestive failure, *per se*.

In asthmatics, too, who are always conscious of their breathing mechanism hyperventilation may develop. Here the syndrome manifests itself when the patient is free of the acute attack and usually while resting.

Having had one episode of pain patients with coronary artery disease are likely to become heart-conscious. Chest pain and dyspnea must be evaluated and hyperventilation ruled out.

In patients prone to syncope from organic causes, Stokes-Adams syndrome or grand or petit mal, anxiety may lead to hyperventilation. Thus a second form of syncope may be superimposed on the first. Several subjects in this study with proved Stokes-Adams syndrome responded to medication only to have an unexpected relapse. Examination during the new attacks of syncope revealed no change in the heart rate or rhythm but a marked change in the character of the breathing. Hyperventilation had developed.

Carotid sinus stimulation has caused one patient to faint. Observation during the episode revealed the onset of deep, sighing-like breaths during the stimulation followed by immediate fainting. When the patient was instructed to hold his breath and the carotid sinus was again stimulated, syncope did not recur. In the same patient severe pressure over the styloid processes (Libman test) caused hyperventilation and fainting. Painful pinching of the fingers gave a similar effect. Here pain which also occurred with carotid sinus stimulation induced hyperventilation and syncope.

The numbness and tingling, lateral nystagmus (of which one case has been observed), pressing or tight headaches, and giddiness suggested space-occupying lesions in the head. The results of neurologic con-

sultations have consistently revealed a pattern so bizarre that a hysterical phenomenon was usually and correctly incriminated.

Because the hyperventilation syndrome may occur in one of ten cases coming to the average physician's office, a high sense of awareness must be inculcated in those of us who see these patients. Only by recognizing the protean manifestations of this very common syndrome will we be able to overcome its effects.

SUMMARY

The symptom patterns of the hyperventilation syndrome have been discussed. Attention has been called to the high incidence of the syndrome. An attempt has been made to correlate these symptoms and the physiologic processes responsible for them. A method of therapy has been outlined. Pitfalls in diagnosis have been noted.

REFERENCES

1. Grant, S. B. and Goldman, A. A study of forced respiration; experimental production of tetany. *Am. J. Physiol.*, 52: 209–232, 1920.
2. Kerr, W. J., Dalton, J. W. and Gliebe, P. A. Some physical phenomena associated with the anxiety states and their relation to hyperventilation. *Ann. Int. Med.*, 11: 962–992, 1937.
3. Carryer, H. M. The hyperventilation syndrome. *M. Clin. North America*, 31: 845–849, 1947.
4. McKell, T. E. and Sullivan, A. J. Hyperventilation syndrome in gastroenterology. *Gastroenterology*, 9: 6–16, 1947.
5. Engel, G. L., Ferris, E. B. and Logan, M. Hyperventilation: analysis of clinical symptomatology. *Ann. Int. Med.*, 27: 683–704, 1947.
6. Wood, P. DaCosta's syndrome. *Brit. M. J.*, 1: 767–772, 805–811, 845–851, 1941.
7. Cannon, W. B. Mechanism of emotional disturbance of bodily functions. *New England J. Med.*, 198: 877–884, 1928.
8. Stead, E. A., Jr. and Warren, J. V. Clinical significance of hyperventilation. *Am. J. M. Sc.*, 206: 183–190, 1943.
9. Friedman, M. Functional Cardiovascular Disease, p. 25. Baltimore, 1947. Williams & Wilkins Co.
10. Friedman, M.,[9] p. 42.
11. Friedman, M.,[9] p. 38.
12. Friedman, M.,[9] p. 38.
13. Friedman, M. Studies concerning the etiology and pathogenesis of neurocirculatory asthenia. IV. The respiratory manifestations of neurocirculatory asthenia. *Am. Heart J.*, 30: 557–566, 1945.
14. White, Paul D. Heart Disease. New York, 1944. Macmillan Co.
15. Davis, H. and Davis, P. The electrical activity of the brain: its relation to physiological states and to states of impaired consciousness. *A. Research Nerv. & Ment. Dis., Proc.*, 19: 50–80, 1939.
16. Gibbs, F. A., Gibbs, E. L. and Lennox, W. G. Electroencephalographic response to overventilation and its relation to age. *J. Pediat.*, 23: 497–505, 1943.
17. Best, C. H. and Taylor, N. B. Physiological Basis of Medical Practice. 4th ed. P. 350–361. Baltimore, 1945. Williams and Wilkins.
18. McDowall, R. J. S. The effect of CO_2 on the circulation. *J. Physiol.*, 70: 301–315, 1930.
19. Davis, H. and Wallace, W. M. Factors affecting changes produced in electroencephalogram by standardized hyperventilation. *Arch. Neurol. & Psychiat.*, 47: 606–625, 1942.
20. Darrow, C. W. and Pathman, J. H. Relation of heart rate to slow waves in the electroencephalogram during overventilation. *Am. J. Physiol.*, 140: 583–588, 1944.
21. Friedman, M.,[9] p. 50.
22. Rubin, M. A. and Turner, E. Blood sugar level and influence of hyperventilation on slow activity in EEG. *Proc. Soc. Exper. Biol. & Med.*, 50: 270–272, 1942.
23. Ferris, E. B., Stevens, C. D., Webb, J. P. and Engel, G. L. Voluntary breathholding. III. The relation of the maximum time of breathholding to the oxygen and carbon dioxide tensions of arterial blood. *J. Clin. Investigation*, 25: 734–743, 1946.
24. Schultzer, P. and Lebel, H. Spontaneous hyperventilation tetany; report on two cases, including investigations on calcium and ionized calcium in blood serum, outside and during attack. *Acta med. Scandinav.*, 101: 303–314, 1939.
25. Fraser, R. and Sargent, W. Hyperventilation attacks. *Brit. M. J.*, 1: 378–380, 1938.
26. Funther, L. and Greenberg, D. Diffusible calcium of the blood stream in tetany. *Arch. Int. Med.*, 47: 660–673, 1931.
27. Best, C. H. and Taylor, N. B.,[17] p. 480.
28. Freidman, M.,[9] p. 52.
29. Thompson, W. P. The electrocardiogram in the hyperventilation syndrome. *Am. Heart J.*, 25: 372–390, 1943.
30. Soley, M. H. and Shock, N. W. Etiology of the effort syndrome. *Am. J. M. Sc.*, 196: 840–851, 1938.
31. Ryder, H. W., Shaver, M. and Ferris, E. B. Salicylism accompanied by respiratory alkalosis and toxic encephalopathy. *New England J. Med.*, 232: 614–621, 1945.
32. White, P. D. Observations on some tests of physical fitness. *Am. J. M. Sc.*, 159: 866, 1920.

Pulmonary Hypertension in Chronic Pulmonary Emphysema*

CRAIG W. BORDEN, M.D., RUSSELL H. WILSON, M.D., RICHARD V. EBERT, M.D. *and* HERBERT S. WELLS, M.D.

Minneapolis, Minnesota

THAT pulmonary hypertension is frequently associated with pulmonary emphysema has often been suggested largely on the basis of clinical and postmortem evidence. Right axis deviation and roentgenologic evidence of enlargement of the right ventricle, for example, are often found in patients with emphysema. At autopsy there may be hypertrophy of the right ventricle and dilatation of the pulmonary artery.

Direct measurement of right ventricular systolic pressure in patients with chronic pulmonary emphysema by means of right heart catheterization was recently carried out by Bloomfield and co-workers.[1] In six such patients they found that two had normal right ventricular systolic pressures while four showed slight to moderate elevation. The pulmonary arterial diastolic pressure was not measured in their study. The following investigation was carried out in order to obtain this measurement and to correlate pulmonary arterial pressures with the loss in pulmonary function:

METHOD

Twenty-four men with chronic diffuse pulmonary emphysema who were moderately or completely disabled by exertional dyspnea were selected. The average age for the group was fifty-five years. The youngest patient was thirty-three and the oldest seventy.

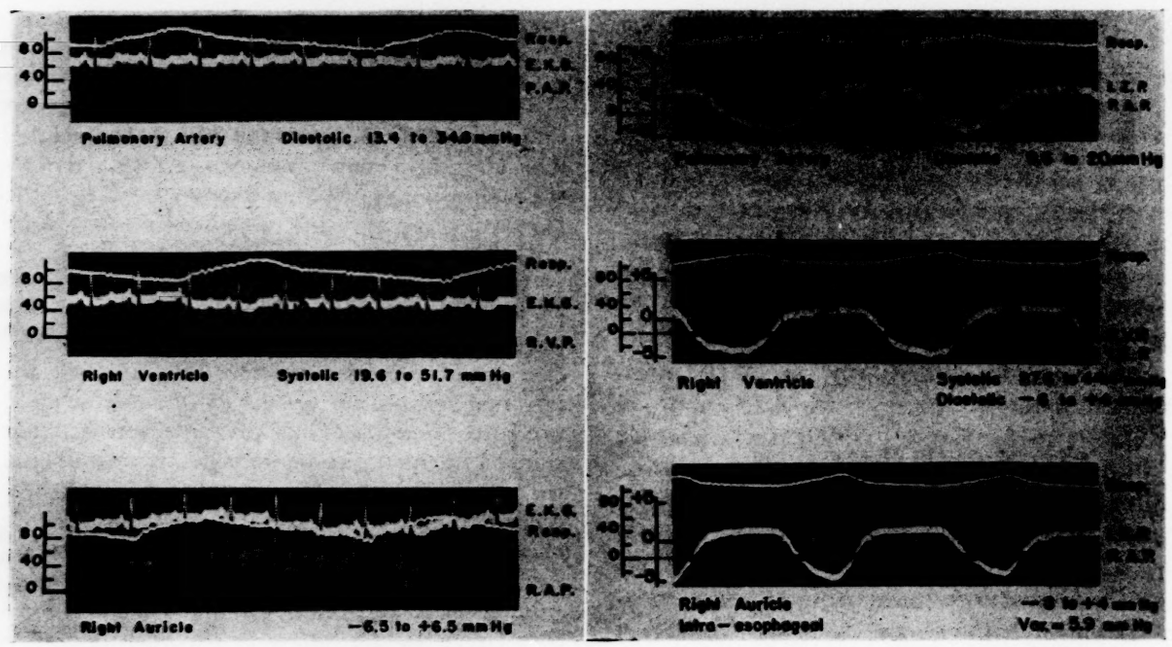
A catheter was inserted into the pulmonary artery.[2,3] Pressures were optically recorded with a Hamilton manometer at numerous points in the pulmonary artery, right ventricle and right atrium.[1,4] The level of the base line was taken to be 10 cm. above the skin of the back.[3,14] The Hamilton manometer was calibrated with an ordinary mercury manometer. Lead II of the electrocardiogram and a pneumogram were recorded simultaneously. (Fig. 2.)

The pressure of each beat in a respiratory cycle, from the peak of one inspiration to the peak of the next inspiration, was measured and the values averaged to take into account the effect of respiration on the pulmonary arterial pressure. Segments of pressure curves that showed the least number of artifacts were chosen for measurement. The systolic pressure was measured on the right ventricular pulse pressure curve from the top of the base line to the top of the level plateau of systole. Artifacts, which frequently occur in the pulmonary arterial pressure curve during systole as the result either of motion of the catheter tip during ventricular ejection or of harmonic vibrations at the natural frequency of the manometer system, are thereby avoided. The diastolic pressure in the pulmonary artery was measured on the pulmonary arterial pressure curve at a point immediately before the beginning of auricular systole and corresponding to the end of ventricular diastasis. A similar point was chosen for measuring the ventricular diastolic pressure. The pressure in the ventricle at the end of the period of diastasis represents the ventricular filling pressure and is equal to the auricular pressure at that moment.[5]

It has been noted previously that attachment of a catheter to the Hamilton manometer reduces the natural frequency of the system.[1,3] The natural frequency of the manometer used in these studies was 110 cycles per second. The

* From the Department of Medicine, University of Minnesota Medical School and the Veterans Administration Hospital, Minneapolis, Minn. Published with permission of the Chief Medical Director, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors. Presented in part at a meeting of the Central Society for Clinical Research, Chicago, Illinois, October 29, 1948.

FIG. 1. Femoral arterial pulse pressure in a normal subject recorded with a Hamilton manometer, (A) through a cardiac catheter attached to an 18 gauge needle and (B) directly through an 18 gauge needle.



2 3

FIG. 2. Pulmonary arterial and intracardiac pressure in emphysema (Subject W. L.). Note the marked respiratory variation. The following symbols are used in the illustration: P.A.P., pulmonary arterial pressure; R.V.P., right ventricular pressure; R.A.P., right auricular pressure; Resp., pneumograph tracing. In the pneumograph tracing the line moves up with inspiration.

FIG. 3. Intra-esophageal pressure (I.E.P.) recorded simultaneously with pulmonary arterial and intracardiac pressure in emphysema (Subject B. B.). The calibration for the former is to the right. The symbols are the same as those in Figure 2.

frequency of the system with a No. 9 French catheter attached to the lead tubing of the manometer fell to 25 cycles per second. To test the validity of the measurements of intravascular pressure with the catheter and the Hamilton manometer, two successive femoral arterial pressure curves were recorded in the same normal subject. The 100 cm. No. 9 French catheter was interposed between the lead tubing of the manometer and the femoral needle; immediately thereafter the catheter was removed and the lead tubing of the manometer was attached directly to the 18 gauge femoral needle. The average pressure with the catheter in place (Fig. 1A) was 130 mm. Hg systolic and 62 mm. Hg diastolic, while that taken without the interposed catheter (Fig. 1B) was 134 mm. Hg systolic and 65 mm. Hg diastolic. The mean pressures determined by planimetric integration were 87.2 mm. Hg and 88.3 mm. Hg, respectively. By inspection the two curves appeared to be quite similar and the contour was not distorted by interposition of the catheter. Dexter and co-workers[3] have reported that pressures in the ventricle of dogs obtained with a Hamilton manometer are identical whether recorded through a catheter or through a No. 18 needle inserted directly into the heart. Hence the recording of intravascular pressure through a catheter by means of a Hamilton manometer seems sufficiently accurate for all but the most exacting research purposes.

A sample of mixed venous blood from the pulmonary artery was collected through the catheter and a sample of arterial blood was obtained by direct puncture of the femoral artery. The blood was collected in an oiled syringe containing a few drops of heparin. These samples of blood were analyzed for oxygen content by the manometric method of van Slyke and Neill[6] and the arteriovenous oxygen difference was calculated. The oxygen capacity was determined on the femoral arterial sample[6] and the per cent saturation was calculated. The expired air was collected in a Tissot spirometer for a period of six minutes and a specimen was analyzed for per cent composition of gases.[6] From these values the oxygen consumption in cubic centimeters per minute was determined. Both the oxygen consumption and the arteriovenous oxygen difference were determined when the patient was in a resting, postabsorptive state, but the measurements were not made simultaneously. For this reason calculation of the cardiac output by the Fick[7] principle was omitted.

The severity of the emphysema was estimated by measuring the total lung volume and its subdivisions. The vital capacity was measured in the supine position with a recording spirometer as described by Christie.[8] The functional residual air was determined by the open circuit method of Cournand, Baldwin, Darling and Richards.[9] The functional residual air was calculated from the alveolar nitrogen concentration and the volume and the nitrogen content of the expired air at the end of a seven-minute period of breathing 100 per cent oxygen.

In certain patients an attempt was made to estimate the respiratory changes in intrathoracic pressure by following the intra-esophageal pressure. A small rubber T tube was placed in the esophagus with the esophageal end left open. The tube was kept patent by blowing a small amount of air through the tube with a syringe. The intra-esophageal pressure was then recorded through the tubing with a strain gauge manometer. Intra-esophageal pressure qualitatively reflects changes in intrapleural pressure although the two pressures are not always the same in absolute terms.[10] The recording of the intra-esophageal pressure simultaneously with that in the pulmonary artery or right ventricle is nevertheless advantageous in that it permits accurate timing of events in the respiratory cycle. (Fig. 3.)

RESULTS

The available values for pulmonary arterial pressure in normal human beings are given in Table I. The pulmonary arterial diastolic pressure appears to be relatively constant and seldom exceeds 11 mm. Hg in young adults. Unfortunately, there are few observations on subjects in the older age groups.

TABLE I

NORMAL VALUES FOR PULMONARY ARTERIAL AND RIGHT VENTRICULAR PRESSURE

	No. of Subjects	Right Ventricular Systolic (mm. Hg)		Pulmonary Arterial Diastolic (mm. Hg)	
		Average	Range	Average	Range
Bloomfield, R. A. et al.[1]	14	25	18–30		
Cournand, A. *Bull. New York Acad. Med.*, 23: 27, 1947.	4	25		8	
Dexter, L. et al. *J. Clin. Investigation*, 26: 554, 1947.	3	26	20–32	10	8–12
Motley, H. L. et al. *Am. J. Physiol.*, 150: 315, 1947.	5	22		6	
Riley, R. L. et al. *Am. J. Physiol.*, 152: 372, 1948.	3	20		9	
Borden, C. W. *Minnesota Med.*, 31: 1218, 1948.	12	20.1	11–26	8.8	6–11

In twenty-four patients with pulmonary emphysema the pulmonary arterial diastolic pressure was found to be distinctly elevated. (Table II.) The mean diastolic pressure was 22 ± 7 mm. Hg, and the range was 15 to 37 mm. Hg. The systolic pressure was elevated in the majority of the twenty-four patients. Eight patients had systolic pressures under 30 mm. Hg, a figure which is within the normal range. Six patients had pressures between 30 and 35 mm. Hg which can be considered slightly elevated. Three patients showed marked elevations in systolic pressures to 50 mm. of Hg or more. The mean systolic pressure for the group of twenty-four subjects was 37 ± 13 mm. Hg, and the range was 23 to 71 mm. Hg. The mean right ventricular diastolic pressure for the group of patients with emphysema and without previous heart failure was 3.8 mm Hg as compared with 4.6 mm. Hg in the patients with emphysema and previous

heart failure. The value for twelve normal subjects was 2.9 mm. Hg. Statistical analysis revealed no significant difference among the ventricular diastolic pressures in these three groups.

greater in the patients with emphysema than in the other two groups and is greater in the pulmonary artery than in the right atrium. Figures 2 and 3 illustrate intravascular pressure tracings in patients with

TABLE II

Subject	Surface Area (sq. m.)	Vital Capacity (cc.)	Residual Air (cc.)	Total Lung Volume (cc.)	Oxygen Consumed (cc./min.)	Oxygen Content Femoral Arterial Blood (vol. per cent)	Oxygen Saturation Femoral Arterial Blood (per cent)	Arteriovenous Oxygen Difference (vol. per cent)	Pressure in mm. Hg			Respiratory Variation in Pressure in mm. Hg		
									Right Ventricular Systolic	Pulmonary Arterial Diastolic	Right Ventricular Diastolic	Right Ventricular Systolic	Pulmonary Arterial Diastolic	Right Auricular
T. A.	1.90	1,020	6,080	7,100	275	17.26	81.5	4.42	23	15	1	12	11	16
O. E.	1.85	2,330	2,010	4,340	...	15.09	89.3	....	25	15	4	9	14	7
J. C.	1.42	2,400	4,270	6,670	215	16.46	86.5	5.16	26	16	0	15	15	5
W. C.	1.64	2,550	3,800	6,350	262	14.65	80.9	4.46	26	18	1	13	12	6
P. W.	1.74	1,290	2,600	3,890	261	18.83	88.1	6.13	27	17	6	27	17	19
V. W.	1.92	2,150	5,910	8,060	285	16.85	90.7	4.74	27	17	4	9	10	..
H. S.	1.78	1,820	5,070	6,890	258	18.82	94.3	5.06	29	19	7	9	15	8
W. A.	1.97	2,150	4,230	6,380	279	16.05	69.8	3.72	29	22	5	13	10	6
W. P.	1.70	2,480	3,530	6,010	239	15.99	90.8	3.76	31	17	1	9	5	3
G. E.	1.74	2,460	4,940	7,400	218	15.79	87.5	4.70	31	20	6	8	15	8
F. M.	1.90	1,420	4,320	5,740	376	19.21	85.7	5.27	31	22	5	22	20	8
W. S.	1.49	1,500	3,270	4,770	199	14.73	71.7	4.39	32	20	4	8	22	6
J. P.*	1.82	1,300	2,640	3,940	211	13.47	86.8	4.00	33	20	2	11	13	10
W. L.	1.72	1,460	3,860	5,320	260	15.35	77.1	4.16	35	26	4	28	19	11
B. B.	1.56	2,100	4,750	6,850	264	14.55	85.0	5.62	36	14	2	17	10	12
T. C.*	1.83	2,250	2,230	4,480	258	14.78	73.6	5.02	36	21	4	15	13	9
M. S.	1.69	2,480	4,350	6,830	159	17.02	86.0	4.58	36	22	6	5	7	3
G. J.*	1.68	1,730	5,350	7,080	269	14.50	61.6	3.70	37	23	1	13	10	11
J. S.*	1.36	1,160	2,390	3,550	197	12.46	68.8	3.53	40	23	7	22	13	14
P. J.	1.58	2,050	5,100	7,150	244	16.55	74.9	3.49	44	23	5	11	11	7
P. O.*	1.72	....	....	....	285	16.65	75.5	3.60	48	34	2	21	20	14
L. M.*	1.50	1,350	3,400	4,750	264	16.10	74.7	5.91	62	28	7	4	5	7
S. W.*	1.66	2,540	3,380	5,920	223	14.45	65.3	4.94	65	34	8	20	14	11
A. B.*	1.92	1,030	4,990	6,020	331	17.32	78.2	5.44	71	37	6	33	18	12
Mean	1.71	1,870	4,020	5,890	254	15.96	80.2	4.60	37	22	4.1	15	13	9

* Patients who had had definite evidence of right heart failure

A striking feature of the records of vascular pressures in patients with pulmonary emphysema is the marked respiratory variation in pressure. Table III gives the mean respiratory variation in pressure in the right atrium, right ventricle and pulmonary artery in the group of patients with emphysema and, for comparison, corresponding values in a group of normal subjects and a group of patients with left ventricular failure. The respiratory variation in pressure is much

pulmonary emphysema. At the onset of inspiration there is a sharp fall in the pulmonary diastolic pressure. The ventricular pulse pressure at the onset of inspiration is low but is markedly increased in the subsequent beat. A corresponding rise in pulmonary arterial diastolic pressure occurs. As shown in Figure 2, the ventricular pulse pressure declines toward the end of expiration and there is an associated decline in pulmonary arterial diastolic pressure. The

atrial pressure falls with inspiration and returns to a positive value at the onset of expiration.

One of the purposes of the study was to determine the relationship, if any, between the degree of pulmonary hypertension in emphysema and the loss in pulmonary function. (Table II.) No correlation was found between the severity of the emphysema, as estimated by the ratio of residual air to total lung volume, and the elevation of pulmonary arterial pressure (r = .1628). There was, however, a significant negative correlation between the oxygen saturation of the arterial blood and the degree of pulmonary hypertension. (Fig. 4.)

TABLE III
MEAN RESPIRATORY VARIATION IN PRESSURE

	Normal	Left Ventricular Failure	Emphysema
No. of patients	12	13	24
Right ventricular systolic (mm. Hg)	3.3	5.3	15
Pulmonary arterial diastolic (mm. Hg)	2.6	4.9	13
Right atrial (mm. Hg)	1.2	2.4	9

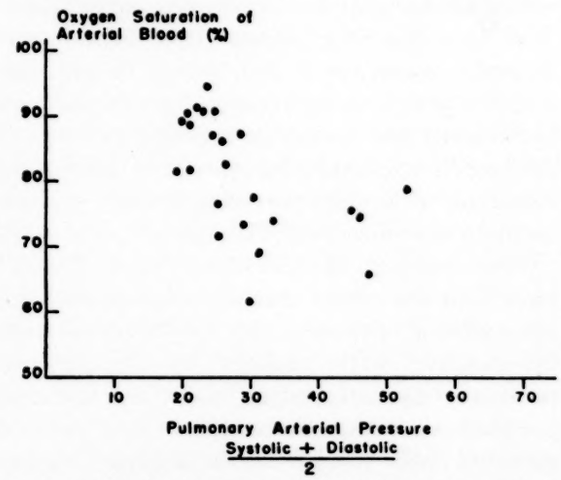


FIG. 4. Chart showing the correlation between pulmonary arterial pressure and oxygen saturation of arterial blood in the individual cases of emphysema (r = −.5563).

The mean arteriovenous oxygen difference in the twenty-four patients with emphysema was 4.6 ± 0.76 volumes per cent. This may be compared with a value of 3.85 ± 0.50 volumes per cent in twelve normal subjects previously studied[11] and 4.5 ± 0.7 volumes per cent obtained by Cournand and co-workers in thirteen normal subjects.[2] The oxygen consumption in the patients with emphysema was normal. There was no significant correlation between the arteriovenous oxygen difference and the degree of oxygen unsaturation of the arterial blood. (Fig. 5.)

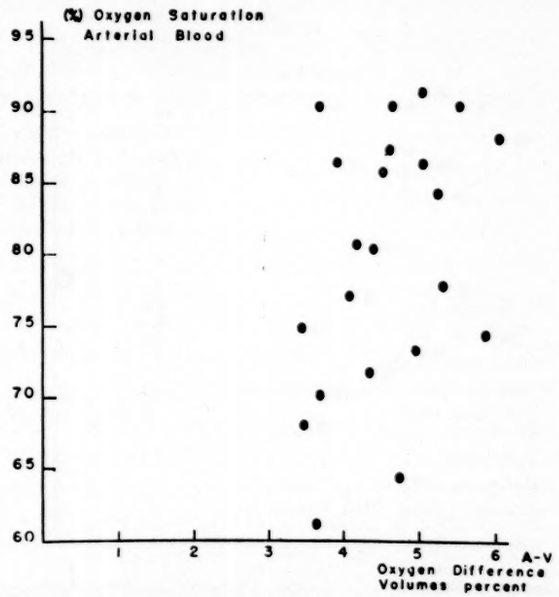


FIG. 5. Chart showing relationship between arteriovenous oxygen difference and oxygen saturation of arterial blood (r = .3597).

Right heart failure, as defined by massive edema, hepatomegaly and markedly elevated systemic venous pressure, occurred in eight of the twenty-four patients. The eight patients were studied after recovery from failure by the same methods as were the sixteen who had not been in failure. (Table IV.) The ratio of residual air to total lung volume was essentially the same in the two groups, as was the arteriovenous oxygen difference. The oxygen saturation was distinctly lower and the pulmonary arterial pressure distinctly higher in the group of patients who had previously had symptoms

of right heart failure. The differences between these means were highly significant when analyzed with the usual statistical methods. The values in the eight patients with previous heart failure for arteriovenous oxygen difference, arterial oxygen saturation and right ventricular systolic pressure were similar to those reported by Richards in six cases of cor pulmonale in failure.[12]

TABLE IV
COMPARISON OF TWO GROUPS OF PATIENTS WITH EMPHYSEMA

	Without Previous Right Heart Failure	With Previous Right Heart Failure
No. of patients	16	8
$\frac{\text{Residual air}}{\text{Total lung volume}} \times 100$	67.7	67.4
Arteriovenous oxygen difference (vol. per cent)	4.64	4.52
Oxygen saturation of arterial blood (per cent)	83.7	73.1
Pulmonary arterial pressure (mm. Hg) systolic	31	49
Pulmonary arterial pressure (mm. Hg) diastolic	19	28

An analysis of the electrocardiograms of the twenty-four patients with pulmonary emphysema revealed that ten had definite right axis deviation (axis greater than +90 degrees). All of the patients with right axis deviation on the electrocardiogram had a diastolic pressure of 20 mm. Hg or greater. It is of interest that all six patients with systolic pressures of 40 mm. Hg or more showed right axis deviation. High, peaked P waves in leads II and III have been described in pulmonary emphysema. In five of the twenty-four patients the P wave in lead II or III of the electrocardiogram exceeded 2.5 mm. in height. Three of these five patients had systolic pressures of 40 mm. Hg or greater.

COMMENTS

The finding of a definite increase in pulmonary arterial diastolic pressure in a group of patients with moderate to severe pulmonary emphysema is of considerable interest. It indicates that there is an increase in the vascular resistance in the lungs in this disease although inaccurate estimation of the level of the right atrium and an increased intrapleural pressure may account for a part of the observed change.

In this study the level of the right atrium was assumed to be 10 cm. above the skin of the back. By direct roentgenologic observation Richards and co-workers[13] showed that a point 10 cm. above the surface of the back corresponds closely to the true level of the right atrium in normal persons. Because of the altered contour of the chest in emphysema it is possible that the spatial relationship of the right atrium to this arbitrary point may differ from that in the normal chest. Lyons, Kennedy and Burwell,[14] however, have produced anatomic evidence that this relationship is affected very little by changes in contour of the chest. The fact that the mean right ventricular diastolic pressure in the group of patients without previous right heart failure differed little from the value in normal persons is also evidence that the arbitrary choice of this base line did not introduce a serious error in pressure measurements.

The studies of Christie[15] and Paine[16] have shown that during expiration the intrapleural pressure in emphysema may be positive with respect to atmospheric pressure. By integrating their intrapleural pressure curves, the mean intrapleural pressure was found to be slightly higher than that in normal persons. Although an increase in mean intrapleural pressure accounts for a small portion of the pulmonary arterial diastolic hypertension in emphysema, it amounts to only a few millimeters Hg. The remainder, therefore, must be due to an increase in pulmonary vascular resistance.

The cause of the increased vascular resistance in chronic pulmonary emphysema is not well understood. It is generally conceded that there is destruction of a large portion of the capillary bed along with destruction of alveolar septa.[17] Isaakssohn[18]

injected the vessels of the lung in emphysema and found that the capillaries were fewer in number than in normal lungs and that thrombosis of the remaining capillaries was frequent. Involvement of the small arteries by endothelial proliferation or thickening of the intima, as well as atherosclerosis of the larger pulmonary arteries, have been noted by several authors.[19–22] A thorough study, in which the degree of pulmonary hypertension is correlated with the pathologic changes in the arteries and capillaries of the lung, is needed before valid conclusions can be reached concerning the cause of increased pulmonary vascular resistance in emphysema.

The marked respiratory variation in intravascular pressure in patients with emphysema is obviously related to changes in intrathoracic pressure. Because of the hazards of pneumothorax in emphysema, intrapleural pressure was not measured directly in this study. However, Neergaard and Wirz,[23,24] Christie[15] and Paine[16] have demonstrated an abnormally wide fluctuation in intrapleural pressure for a given volume of tidal air in patients with pulmonary emphysema, a finding which they attributed to diminished pulmonary elasticity. The average respiratory fluctuation in intrapleural pressure in eleven patients studied by Paine[16] was 13.1 cm. of water or 9.7 mm. Hg as compared to 5.6 cm. of water or 4.3 mm. Hg in subjects with normal lungs. The mean respiratory variation in the right atrial pressure in patients in the present study was 9 mm. Hg, a value which agrees closely with the mean variation in intrapleural pressure in patients with emphysema observed by Paine. It is apparent, therefore, that the abnormally wide variations in intrathoracic pressure in emphysema are transferred directly to the right atrium. The respiratory variations in the ventricular systolic and pulmonary arterial diastolic pressures were greater than those in the right atrium (Table III) and are similar to those observed in normal subjects during deep breathing. An analysis of these changes has been reported in an excellent study by Lauson and co-workers.[5] Fluctuations in intrathoracic pressure produce variations in ventricular filling and stroke output in accordance with Starling's law. In addition fluctuations in intrathoracic pressure probably alter the resistance in the smaller pulmonary vessels. Because of the multiple factors concerned the exact contribution of a variable vascular resistance to the observed respiratory changes in pulmonary arterial and ventricular pulse pressures cannot be ascertained at the present time.

Recent studies of cor pulmonale in emphysema have emphasized the frequency of enlargement of the right heart in patients dying of this disease.[25–28] In the present study the group of patients with obvious right heart failure had an average pulmonary arterial pressure which was significantly higher than the group of patients without right heart failure. It is apparent, therefore, that the pulmonary hypertension contributed to right heart enlargement and failure. Other factors to be considered in the pathogenesis of right heart failure in emphysema are hypoxemia and retention of carbon dioxide. The fact that the group of patients with previous right heart failure had a significantly greater degree of hypoxemia than the group without heart failure (Table IV) and the observation that right heart enlargement occurs at high altitude[29] suggest that decreased oxygen tension in the arterial blood is implicated in the etiology of cor pulmonale and right heart failure. Retention of carbon dioxide with respiratory acidosis in severe emphysema may also impair cardiac function.

It has been suggested that heart failure complicating pulmonary emphysema is characterized by a high cardiac output consequent to a low arterial and tissue oxygen tension.[30–33] Judging from the arteriovenous oxygen difference of 4.52 volumes per cent the cardiac output in those patients with previous right heart failure was normal. Moreover, no significant correlation was found between the oxygen saturation of the arterial blood and the arteriovenous oxygen difference in those patients with emphysema.

Hence there is no evidence from this study that patients with emphysema compensate for their hypoxemia by an increase in cardiac output.

SUMMARY

1. A significant elevation of pulmonary arterial diastolic pressure was found in twenty-four patients with chronic pulmonary emphysema. Systolic pressure was also elevated in the majority of these patients. Evidence is presented which indicates that pulmonary hypertension in emphysema is related to an increased vascular resistance in the lungs.

2. Marked respiratory variation is the outstanding characteristic of intravascular and intracardiac pressure records in patients with emphysema. This depends upon abnormally wide fluctuations in intrathoracic pressure.

3. There is no correlation between the degree of pulmonary hypertension and severity of the emphysema as estimated by the altered ratio of residual air to total lung volume.

4. Eight of the twenty-four patients with emphysema had definite evidence of right heart failure prior to study. The pulmonary arterial pressure was significantly higher and the oxygen saturation of the arterial blood was significantly lower in this group than in the group of sixteen patients with emphysema uncomplicated by right heart failure.

5. The mean arteriovenous oxygen difference in twenty-three patients with pulmonary emphysema was similar to that reported for normal subjects. No evidence was found to indicate that oxygen unsaturation of the arterial blood in emphysema induces an increase in the output of the heart.

REFERENCES

1. Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S. and Richards, D. W., Jr. Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardio-circulatory disease. *J. Clin. Investigation*, 25: 639, 1946.

2. Cournand, A., Riley, R. L., Breed, E. S., Baldwin, E. de F. and Richards, D. W. Measurement of cardiac output in man using the technique of catheterization of the right auricle or ventricle. *J. Clin. Investigation*, 24: 106, 1945.

3. Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Siebel, R. E. and Evans, J. M. Studies of congenital heart disease. I. Technique of venous catheterization as a diagnostic procedure. *J. Clin. Investigation*, 26: 547, 1947.

4. Hamilton, W. F., Brewer, G. and Brotman, I. Pressure pulse contours in the intact animal. I. Analytical description of a new high frequency manometer. *Am. J. Physiol.*, 107: 427, 1934.

5. Lauson, H. D., Bloomfield, R. A. and Cournand, A. The influence of the respiration on the circulation in man. *Am. J. Med.*, 1: 316, 1946.

6. Peters, J. P. and Van Slyke, D. D. Quantitative Clinical Chemistry. Vol. 2, Methods. Baltimore, 1943. Williams & Wilkins.

7. Fick, A. Ueber die Messung des Blutquantums in den Herzventrikeln. *Verhandl. d. physical. med. Gesellsch. z. Würzburg*, 2: 16, 1870.

8. Christie, R. V. The lung volume and its subdivisions. I. Methods of measurement. *J. Clin. Investigation*, 11: 1099, 1932.

9. Cournand, A., Baldwin, E. de F., Darling, R. C. and Richards, D. W., Jr. Studies of intrapulmonary mixture of gases. IV. The significance of the pulmonary emptying rate and a simplified open circuit measurement of residual air. *J. Clin. Investigation*, 20: 681, 1941.

10. Wilson, R. H., Falk, A. and Wells, H. S. Unpublished data.

11. Ebert, R. V., Borden, C. W., Wells, H. S. and Wilson, R. H. Studies of the pulmonary circulation. I. The circulation time from the pulmonary artery to the femoral artery and the quantity of blood in the lungs in normal individuals. *J. Clin. Investigation*, 28:1134, 1949.

12. Richards, D. W., Jr. Cardiac output by the catheterization technique in various clinical conditions. *Federation Proc.*, 4: 215, 1945.

13. Richards, D. W., Jr., Cournand, A., Darling, R. C., Gillespie, W. H. and Baldwin, E. de F. Pressure of blood in the right auricle in animals and in man: under normal conditions and in right heart failure. *Am. J. Physiol.*, 136: 115, 1942.

14. Lyons, R. H., Kennedy, J. A. and Burwell, C. S. Measurement of venous pressure by direct method. *Am. Heart J.*, 16: 675, 1938.

15. Christie, R. V. The elastic properties of the emphysematous lung and their clinical significance. *J. Clin. Investigation*, 13: 295, 1934.

16. Paine, J. R. The clinical measurement of pulmonary elasticity. A comparison of the methods of Christie and McIntosh and of Neergaard and Wirz. *J. Thoracic Surg.*, 9: 550, 1940.

17. Christie, R. V. Emphysema of the lung. *Brit. M. J.*, 1: 105, 1944.

18. Isaakssohn. Pathological-anatomische Veränderungen der Lungengefässe beim Emphysem. *Virchows Arch. f. path. Anat.*, 53: 466, 1871.

19. Ljundahl, M. Untersuchungen ueber die Arteriosklerose des kleinen Kreislaufs. Wiesbaden, 1915. J. F. Bergmann.

20. BRENNER, O. Pathology of the vessels of the pulmonary circulation. Part II. Diseases of the pulmonary vessels. *Arch. Int. Med.*, 56: 457, 1935.
21. PARKINSON, J. and HOYLE, C. The heart in emphysema. *Quart. J. Med.*, 6: 59, 1937.
22. PARKER, R. L. Pulmonary emphysema. A study of its relation to the heart and pulmonary arterial system. *Ann. Int. Med.*, 14: 795, 1940.
23. v. NEERGAARD, K. and WIRZ, K. Ueber eine Methode zur Messung der Lungenelastizität am lebenden Menschen, insbesondere beim Emphysem. *Ztschr. f. klin. Med.*, 105: 35, 1927.
24. v. NEERGAARD, K. and WIRZ, K. Die Messung der Strömungswiderstände in den Atemwegen des Menschen insbesondere bei Asthma und Emphysem. *Ztschr. f. klin. Med.*, 105: 51, 1927.
25. KOUNTZ, W. B., ALEXANDER, H. L. and PRINZMETAL, M. The heart in emphysema. *Am. Heart J.*, 11: 163, 1936.
26. SCOTT, R. W. and GARVIN, C. F. Cor pulmonale: observations in fifty autopsy cases. *Am. Heart J.*, 22: 56, 1941.
27. RIGLER, L. G. and HALLOCK, P. Chronic cor pulmonale. *Am. J. Roentgenol.* 50: 453, 1943.
28. SPAIN, D. M. and HANDLER, B. J. Chronic cor pulmonale. Sixty cases studied at necropsy. *Arch. Int. Med.*, 77: 37, 1946.
29. ROTTA, A. Physiological condition of the heart in the natives of high altitudes. *Am. Heart J.*, 33: 669, 1947.
30. MCMICHAEL, J. and SHARPEY-SCHAFER, E. P. The action of intravenous digoxin in man. *Quart. J. Med.*, 13: 123, 1944.
31. MCMICHAEL, J. Circulatory failure. *Schweiz. med. Wchnschr.*, 76: 851, 1946.
32. SHARPEY-SCHAFER, E. P. 2-Thiouracil in the treatment of congestive heart failure. *Brit. M. J.*, 2: 888, 1946.
33. MCMICHAEL, J. Study of Circulatory Failure by Venous Catheterization. Advances in Internal Medicine. Vol. 2, p. 64. New York, 1947. Interscience Pub., Inc.

The Role of Nitrogen Mustard Therapy in the Treatment of Lymphomas and Leukemias*

CHARLES L. SPURR, M.D., TAYLOR R. SMITH, M.D.,
Houston, Texas *Boston, Massachusetts*

MATTHEW BLOCK, M.D. *and* LEON O. JACOBSON, M.D.
Chicago, Illinois

THIS is a report of the results of nitrogen mustard therapy in lymphomas and leukemias after five years' observation. The use of this compound for chemotherapy in malignant dyscrasias of the hemopoietic system developed during the recent war and considerable clinical information was collected before security measures permitted publication.[1] Methyl bis β-chloroethyl amine hydrochloride and the tris analog have been of greatest interest. Extensive studies of the mechanism of action and pathologic effects in animals and humans have been reported. These have described the enzyme-inhibiting properties of the compounds,[2,3] their ability to arrest mitosis[4] and to produce mutations in lower forms of life.[5] The pathologic effects of the compounds upon various tissues and, in particular, their proclivity for the rapidly proliferating "tissues" of the hemopoietic system and intestinal tract have been explored.[6,7] Efforts have been made to correlate the pathologic lethal effects with alterations in fluid balance, immunology and, at higher doses, neurogenic influences.[8]

The clinical application of nitrogen mustard was reviewed in reports by Goodman et al.,[10] Jacobson et al.,[11] Karnofsky et al.[12] and Wintrobe et al.[13] These demonstrated the value of this form of therapy in the lymphomas and leukemias and suggested that other tumors might be responsive. Through a cooperative plan of the Committee on Growth, National Research Council, methyl bis β-chloroethyl hydrochloride was made available to the profession for supervised trial.[9] These studies have offered further evidence of immediate clinical benefits but we are unaware of any cases observed over an extended period.

The problems associated with dosage and the hematologic reaction have been discussed by Spurr et al.,[14] Karnofsky et al.[15] and Zanes et al.[16] Over the past four years dosage has been standardized in this group for the purpose of gaining information on the use of the material in controlling lymphomas. The alleviation of symptoms in early and advanced cases which were no longer responding to roentgen therapy has been of sufficient promise to warrant careful consideration of the use of this compound in the control of the disease process.

In this period of study we have attempted to use nitrogen mustard therapy in repeated courses and have resorted to roentgen therapy for the control of local masses when necessary. If the disease was widespread and without a major focus, we have not used roentgen therapy. A report of the comparative ability of nitrogen mustard and roentgen therapy to influence the course of the disease may be of use at this time in planning additional extended studies.

* From the Department of Medicine, University of Chicago, Chicago, Ill. This work was supported in part by a Grant-in-Aid from the American Cancer Society, upon the recommendation of the Committee on Growth of the National Research Council.

METHODS AND CLINICAL MATERIAL

A total of ninety-five cases is included in this report. There are fifty-seven cases of Hodgkin's disease, ten of lymphosarcoma, ten of chronic lymphatic leukemia, five of follicular lymphoblastoma, six of chronic myeloid leukemia, five of acute leukemia and two of reticulum cell sarcoma.

TABLE I
RATING SCHEDULE FOR NITROGEN MUSTARD THERAPY

	Failure	Poor	Fair	Good
Duration of remission after single courses (wk.)	4	4–6	6–8	8–10
Duration of effective HN_2 therapy (mo.)	3	4–6	6–12	12
Survival from initiation of HN_2 therapy (mo.)	6*	6–12†	12–24†	24+†

* No significant clinical remission although there may be some resolution of lymphadenopathy and alleviation of symptoms.
† At least 50 per cent of the survival period the patient was able to carry out normal duties.

We have classified the cases of Hodgkin's disease on the basis of pretreatment biopsy of lymph nodes, using the criteria of Jackson and Parker.[17] There are six cases showing the microscopic picture of the paragranulomatous type in lymph nodes but presenting a clinical picture characteristic of Hodgkin's granuloma. Later, microscopic study of lymph node biopsies in two cases showed granulomatous disease. We have, therefore, included these six in our discussion as granulomas. There are thirty-four cases of the classical granulomatous type and seventeen cases of Hodgkin's sarcoma. Each case was evaluated by lymph node biopsy, bone marrow and peripheral blood studies as stated in the protocol of our earlier reports.[11,14]

The dose of methyl bis β-chloroethyl amine hydrochloride employed throughout this study was 0.1 mg. per kg. of body weight. There was some variation in the frequency and number of intravenous injections but most patients received the standard course of four consecutive daily injections. Care was taken that an evaluation of the status of each case, before and after treatment, was made by physical examination and radiographic and blood studies. Peripheral blood counts were made regularly in the four weeks following therapy and special care was exercised to evaluate the status of the patient throughout any leukopenic phase. The changes in peripheral blood and bone marrow have been adequately covered in earlier reports.[11,13,14,16,31] The recurrence of lymphadenopathy, splenomegaly, anemia or other systemic symptoms has been considered indicative of relapse and treatment was usually reinstituted within ten days. In several cases local masses were irradiated, as mentioned in protocols.

An evaluation of the response of this group of diseases to nitrogen mustard therapy should consider not only the survival following the onset of disease but also the clinical status of the patient throughout his period of observation. Hence, an effort should be made to evaluate the response by a classification which includes: (1) the duration of remissions following each course of treatment, (2) the duration of effective nitrogen mustard therapy and (3) the period of survival and normal activity following initiation of nitrogen mustard therapy. On the basis of the duration of each of these periods we may develop a definition of our qualifying terms: *failure*, *poor*, *fair* and *good*. This classification (Table I) has been used in evaluating each case. The requirements are stringent in comparison to those commonly applied in the therapy of lymphomas since remissions have been frequently cited as the time elapsing between treatments.

RESULTS

A definitive statement of the role nitrogen mustard may play in the control of the lymphomas and leukemias will be possible only after a large number of cases have been followed through the course of their disease but data now available are sufficient to explore its proper use. Each case is cited individually in tabular form (Table II) with the information pertinent to this discussion. This includes generic data, major involvement or manifestation, duration of disease prior to treatment with nitrogen mustard, period of roentgen therapy and response, with similar data for nitrogen mustard therapy. Also, we have shown the total duration of the disease and present status. The cases included in our first report[11] are indicated in Table II since they were observed over the longest period.

The relative responsiveness of the lymphomas to nitrogen mustard therapy is shown on Table V, distributed according to the schedule presented in Table I. There is

TABLE II

SUMMARY OF THE CLINICAL COURSE OF INDIVIDUAL CASES WITH LYMPHOMAS AND LEUKEMIA UNDER ROENTGEN AND NITROGEN MUSTARD THERAPY

Case and Unit No.	Age	Sex	Major Involvement	Duration Prior to Therapy (mo.)	Duration of Roentgen Therapy (mo.)	Duration Prior to HN_2 Therapy (mo.)	Nitrogen Mustard Therapy				Period of Observation (mo.)	Total Duration or Duration to Date (mo.)	Present Status (Living or Dead)	Results Rating
							No. of Courses	Average Dose Per Course (mg.)	Average Remission (mo.)	Duration of Effective HN_2 Therapy (mo.)				
Hodgkin's "Paragranuloma"														
1. 347165	48	F	Adenopathy, anemia	24	48	72	6	21	4.5	36	48	120	L*	Good
2. 181790	29	F	Adenopathy (mediastinum)	10	....	10	4	22	3.	12	40	72	L*	Good
3. 385104	27	F	Adenopathy (abdomen)	37	....	37	2	24.2	4.5	10	16	53	L	Good
4. 389349	38	F	Adenopathy, pruritus	20	36	56	1	23.6	18	18	24	80	L	Good
5. 332798	55	M	Adenopathy	6	36†	42	9	27	2.5	30	32	74	D*	Good
6. 276499	47	M	Adenopathy	9	36†	44	2	24.8	12	27	34	88	L	Good
Average	..	..	.....	18	39	43	4	24	7.4	22.1	32.3	81	5L 1D	.....
Hodgkin's Granuloma														
7. 348546	26	M	Adenopathy (pulmonary, mediastinum)	6	....	6	3	29	1.0	5	6	12	D*	Failure
8. 410710	31	M	Adenopathy, Pel-Ebstein fever	6	0†	6	1	26.8	1.5	1.5	4	10	D	Failure
9. 323331	32	M	Adenopathy, bone (osteolytic)	8	30†	8	2	33.9	3.0	8	8	46	D*	Poor
10. 328860	31	F	Adenopathy (mediastinum)	12	24†	14	7	14.3	1.0	12	18	32	D*	Poor
11. 320439	19	M	Adenopathy (mediastinum)	8	12†	8	6	30.0	1.0	6.0	8.0	12	D*	Poor
12. 350097	36	M	Adenopathy, bone (osteolytic)	10	2†	6.7	3	27.8	1.4	6.7	8	14.7	D*	Poor
13. 366351	23	M	Adenopathy (mediastinum)	8	....	2.5	3	27.8	.66	2.5	5	30	D	Poor
14. 323396	48	F	Adenopathy (abdomen)	12	....	10	2	35.6	5.0	9.	6	16	D*	Poor
15. 409460	37	F	Adenopathy (pulmonary)	3	8	5	2	27.0	1.5	3	5	10	D	Poor
16. 398305	24	M	Adenopathy, fever	9	20†	29	2	30.0	1.8	3.5	7	36	D	Poor
17. 341183	44	F	Adenopathy (mediastinum, retroperitoneal, spleen)	10	36†	52	3	38.0	1.5	4.5	5	57	D	Poor
18. 304793	19	M	Adenopathy	6	10+	18	13	24.0	2.7	52	60	78	D*	Good
19. 219178	36	M	Adenopathy	6	24	30	6	23.4	1.7	12	15	45	D*	Fair
20. 370828	28	M	Fever, anemia	6	10†	16	6	25.3	2.8	25	28	44	D*	Fair
21. 335509	36	F	Adenopathy (pulmonary), fever	8	3	11	8	21.8	1.6	18	22	33	D*	Fair
22. 329408	36	M	Adenopathy, gastric distress	8	continuous	44	2	22.4	3.0	12+	14	58	D	Fair
23. 401790	19	F	Adenopathy (mediastinum)	6	....	8	2	29.	5.5	12+	18	26	L	Fair
24. 210156	17	M	Adenopathy (pulmonary), arthritis	16	....	16	5	22	2.2	16	19	35	D*	Fair
25. 308390	23	M	Adenopathy (pulmonary)	6	6	12	11	24	1.6	22	24	36	D*	Fair
26. 327527	20	F	Adenopathy (mediastinum), cough	6	3	9	2	20	3.0	8+	13	46	L	Fair
27. 390654	31	F	Cervical, axillary, mediastinum, pulmonary adenopathy	10	8	18	4	23.1	2.5	12+	20	38	L	Fair
28. 316514	42	M	Mediastinum, fever	18	....	18	19	24.7	2.75	60	60	78	L*	Good
29. 336024	40	M	Adenopathy, fever	4	8	12	9	28.7	2.3	20.5	21	36	D*	Good

TABLE II (*Continued*)

Case and Unit No.	Age	Sex	Major Involvement	Duration Prior to Therapy (mo.)	Duration of Roentgen Therapy (mo.)	Duration Prior to HN_2 Therapy (mo.)	Nitrogen Mustard Therapy				Period of Observation (mo.)	Total Duration or Duration to Date (mo.)	Present Status (Living or Dead)	Results Rating
							No. of Courses	Average Dose Per Course (mg.)	Average Remission (mo.)	Duration of Effective HN_2 Therapy (mo.)				
30. 7706	41	M	Adenopathy, anemia, fever	6	2†	14	11	29.8	1.7	21	24	40	D*	Good
31. 410930	22	M	Adenopathy, anemia, cervical mass	6	8	96	1	18.8	6	12	12	108	L	Good
32. 391785	31	M	Adenopathy, bone	7	84†	105	4	27.4	3.0	20	20	125	D	Good
33. 347623	27	M	Adenopathy (abdomen), liver, spleen	24	24†	24	8	24.5	3.3	40	42	66	L*	Good
34. 326177	24	M	Adenopathy, fever, weight loss	2	12+	14	15	19.3	2.6	46	46	60	L*	Good
35. 398966	27	M	Adenopathy	6	24†	24	3	37.9	4.3	16	20	44	L	Good
36. 395060	28	F	Mediastinal adenopathy, abdominal mass, back pain	4	56+	60	4	19.2	2.5	11	11	71	D	Good
37. 412348	30	M	Adenopathy, fever, anemia, bone	8	21+	21	3	22.6	2.+	12	12	33	L	Good
38. 389630	35	M	Adenopathy	6	96	96	3.	24	5.7	24	24	96	L	Good
39. 357210	28	F	Adenopathy (mediastinum abdomen), spleen, liver, Pel-Ebstein fever	8	60†	60	9	20	2.4	32	36	96	D*	Good
40. 391883	29	M	Adenopathy (abdomen) liver, spleen	8	60+†	70	2	22.6	4+	14	22	92	L	Good
Average	..	..	.....	8.1	24.8	28.6	5.4	25.7	2.6	17.1	19.7	49.1	23D / 11L	.....
Hodgkin's Sarcoma														
41. 371484	17	m	Adenopathy, laryngeal obstruction, mediastinum	3	24	27	4	23.2	1.0	6	6	33	D*	Failure
42. 400791	40	M	Febrile, adenopathy	20	....	20	1	21	.5–1+	0	6	26	L	Failure
43. 411887	51	F	Adenopathy (pulmonary)	6	2	30	1	17.2	1	1	4	34	D	Failure
44. 407339	64	M	Adenopathy (mediastinum, abdomen)	10	12†	22	1	30.0	2.	2	4	26	D	Failure
45. 356742	63	M	Adenopathy (mediastinum, abdomen)	6	12†	16	1	28.0	0	0	2	18	D	Failure
46. 395154	24	M	Adenopathy, pruritus, abdomen, pleural, pulmonary	12	0†	12	2	27.1	0	0	4	16	D*	Failure
47. 397219	39	M	Adenopathy (mediastinum)	6	0†	14	3	32.1	0.75	3.	6	20	D	Failure
48. 406788	56	M	Adenopathy, pruritus, anemia	8	4†	20	2	26.4	0	0	4	24	D	Failure
49. 387481	27	F	Adenopathy (mediastinum)	12	2.5†	16	4	25.1	0.5	6	8	24	D	Poor
50. 309066	23	M	Adenopathy, superior vena cava obstruction, cardiac	9	8†	19	5	29.2	1.0	9	11	30	D	Poor
51. 401690	34	M	Adenopathy, febrile	12	12†	24	2	28.0	2.5	7	8	32	D	Poor
52. 391441	44	F	Adenopathy (pulmonary)	8	28†	36	3.	22.7	1	4	10	46	D	Poor
53. 306582	41	F	Adenopathy (abdomen, pulmonary)	36	12†	48.	3	17.3	2.	5	7	55	D	Poor
54. 318261	32	F	Adenopathy (mediastinum, abdomen)	6	22†	26	3	19.7	1	6	9	35	D	Poor
55. 397847	35	F	Adenopathy (abdominal), pleural	3	10†	14	2	28	1	3	12	26	D	Poor

TABLE II (*Continued*)

Case and Unit No.	Age	Sex	Major Involvement	Duration Prior to Therapy (mo.)	Duration of Roentgen Therapy (mo.)	Duration Prior to HN_2 Therapy (mo.)	Nitrogen Mustard Therapy				Period of Observation (mo.)	Total Duration or Duration to Date (mo.)	Present Status (Living or Dead)	Results Rating
							No. of Courses	Average Dose Per Course (mg.)	Average Remission (mo.)	Duration of Effective HN_2 Therapy (mo.)				
56. 40999	47	F	Adenopathy (cervical, superior mediastinum)	3	36†	39	7	20.3	0.8	13	14	53	D	Poor
57. 365177	31	M	Adenopathy	20	24†	44	7	35.0	1.8	14	18	62	D*	Fair
Average	..	..	.....	15.8	13.0	25.1	3	25.9	1.0	4.6	7.8	32.9	1L16D	.....
Lymphosarcoma														
58. 385271	47	M	Adenopathy, bone (osteolytic), abdominal, spleen, liver	7	....	....	1	32.0	0	0	3	10	D	Failure
59. 410166	67	F	Adenopathy, spleen, liver, abdomen (ascites)	18	12	....	2	21	3	8+	15	33	L	Poor
60. 81913	53	F	Adenopathy (abdomen), liver, spleen, pulmonary	6	3	....	3	17	2.3	10	14	44	D	Poor
61. 103101	60	M	Adenopathy (pulmonary, abdominal)	3	36	....	6	25.7	2.7	22	25	62	D*	Fair
62. 398664	28	F	Adenopathy, weakness	4	....	....	4	28	2.5	12+	20	24	L	Fair
63. 316278	71	F	Adenopathy (abdomen), spleen, liver (ascites)	14	6–8	....	2	13.8	8	16	24	50	D	Fair
64. 329545	30	F	Adenopathy, liver, abdomen, fever	15	....	....	7	18.	6	44+	48	60	L*	Good
65. 343111	55	M	Adenopathy, fever, weight loss	1	....	....	1	29.5	40	53+	58	60	L*	Good
66. 6479	24	F	Adenopathy, abdomen, gastrointestinal, weight loss	12	....	....	11	12.8	4	44	60	72	L*	Good
67. 368128	31	M	Adenopathy	8	24	....	3	27.5	2.7+	14+	16	59	L	Good
Average	..	..	.....	8.8	8.3	....	4	22.5	7.1	22.3	28.3	47.4	6L/4D	.....
Chronic Lymphatic Leukemia														
68. 199390	65	M	Adenopathy (abdominal), spleen, liver, anemia	24	....	11	2	24	0	0	11	36	L	Failure
69. 398007	45	M	Adenopathy (abdominal)	24	....	24	1	32	1	0	4	36	D	Failure
70. 393931	51	F	Adenopathy (abdominal), liver, spleen	....	....	24	1	16.8	0	0	....	36	D	Failure
71. 165322	66	M	Adenopathy, nasopharynx	....	....	24	1	24	2+	3	16	48	L	Failure
72. 343634	63	M	Adenopathy, abdominal mass, rectal stricture	72	....	72	1	27.2	2.5	2.5	12	84	D*	Poor
73. 331471	63	M	Urinary, renal	24	....	24	1	30	5	5	11	36	D*	Poor
74. 312662	64	F	Adenopathy (abdominal), spleen, liver	84	....	108	3	35	2.3	11	16	120	D*	Fair
75. 277335	64	M	Adenopathy abdominal masses, lymph, spleen, pleura	48	....	60	3	29.7	2.3	23	23	84	D*	Fa
76. 342409	41	M	Adenopathy (abdominal), spleen	6	....	6	2	21.7	19	38	54	60	L*	Good
77. 404385	69	M	Adenopathy, purpura	24	....	24	1	27	10	12	16	36	L	Good
Average	..	..	.....	30.6	....	37.7	1.6	26.7	4.4	9.5	16.3	57.6	4L/6D	.....

* Case previously reported.
† "Roentgen-resistant"—no longer responsive to irradiation.

a striking predominance of satisfactory (*fair* or *good*) remissions in the patients with Hodgkin's granuloma as compared with Hodgkin's sarcoma. In this group of cases the response of the lymphosarcomas was satisfactory in 70 per cent of the ten cases followed. We shall comment further on the variable and poor remissions of chronic lymphatic leukemia.

Hodgkin's Disease. In this group of fifty-seven unselected cases of Hodgkin's disease which were under observation two to sixty months, forty are dead and seventeen remain under treatment. It became apparent early in our study that the clinical course of these cases varied greatly, suggesting the advisability of correlating the course with the pathologic picture seen in the pretreatment biopsy. Six cases showed a paragranulomatous biopsy picture although four had had previous x-ray therapy and two had been described as roentgen-resistant after three years of treatment. The data concerning this group are presented separately in Table II but in our survey of survival (Table V) we have included these cases in the granulomatous group of which they are clinically representative. The average remission of 7.4 months following a course of nitrogen mustard and the continuous response for ten to thirty-six months thereafter illustrates the relatively benign course of this group. One patient (Case 5) previously roentgen-resistant succumbed with mediastinal involvement not amenable to irradiation after responding well to nitrogen mustard therapy for thirty months. This is the only case of this group in which it became desirable to use x-ray therapy. The other patients continued to respond for an average of twenty-two months after their first nitrogen mustard treatment.

Hodgkin's Granuloma. There are thirty-three cases with classical granulomatous changes in their pretreatment lymph nodes. The six cases mentioned previously increase the group to thirty-nine. It is of interest to note the wide variety of manifestations which have responded to nitrogen mustard. (Table II.) The response of this group has been satisfactory (*good* or *fair*) in 72 per cent, or twenty-eight cases, while in eleven cases, or 28 per cent, there was poor response. (Table V.) The twenty-four patients who have died responded to nitrogen mustard for 14.7 months and survived an average of 44 months following their first symptoms. (Table III.) There are sixteen patients living who have responded to nitrogen mustard 22.3 months and have a survival to date of 67.6 months. Both groups responded approximately twenty-seven months to irradiation.

Hodgkin's Sarcoma. In contrast to the previously discussed forms of Hodgkin's disease the sarcoma group has been particularly unresponsive. Seventeen cases have been observed for periods of two to eighteen months under nitrogen mustard therapy. Fifteen were no longer responsive to x-ray therapy and in all there was evidence of widespread disease at the time chemotherapy was instituted. (Table II.) Further evidence of the progressive behavior of the disease in this group is derived from the fact that this status had developed despite x-ray therapy over an average of thirteen months. (Table III.) The sixteen patients now dead had an average effective period of nitrogen mustard therapy of 4.8 months and, despite persistent x-ray therapy in 50 per cent of the cases, the total duration of the disease was only thirty-three months. However, it should be mentioned that considerable palliative benefit, in some cases as long as fourteen months, was afforded during the period of nitrogen mustard therapy.

Hodgkin's Disease as a Single Group. The subclassification of Hodgkin's disease is not unanimously accepted. Slaughter and Craver[28] have surveyed 265 cases which they believe show no correlation between the pathologic picture and the clinical course. A comparison of our data with previous reports may be facilitated by recapitulating the results as a single group. (Table III.) There are seventeen patients living and forty who have died. In the latter group the average duration from the appearance of symptoms to death was 39.7

months with a period of effective nitrogen mustard therapy of 11.7 months. Irradiation proved effective for an average of 22.4 months and the average duration of disease to date is 65.1 months.

living and in good health. The average single remission has been 3.5 months if the case with a single five-year remission is excluded. Irradiation was given after beginning nitrogen mustard therapy only to the

TABLE III

SUMMARY OF RESPONSE OF HODGKIN'S DISEASE TO IRRADIATION AND NITROGEN MUSTARD THERAPY

No. of Cases		Duration Prior to Therapy (mo.)	Duration of Roentgen Therapy (mo.)*	Duration Prior to HN_2 Therapy (mo.)	Nitrogen Mustard Therapy				Period of Observation	Total Duration or Duration to Date (mo.)
					No. of Courses	Average Dose Per Course (mg.)	Average Remission (mo.)	Duration of Effective HN_2 Therapy (mo.)		
Hodgkin's Granuloma										
Living	16	12.4	27.38	38.5	4.8	23.8	5.25	22.3	22.3	67.6
Dead	24	7.6	25.8	24.8	5.6	26.8	2.05	14.7	17.1	43.9
Hodgkin's Sarcoma										
Living	1	20.	0	20.	1.	31.	.5–1+	.5–1.+	6	26
Dead	16	10.	14.9	25.4	3.5	25.6	1.25	6.0	7.9	33.4
All Hodgkin's Cases										
Living	17	12.9	22.9	37.4	4.5	24.3	5.0	22.4	26.9	65.1
Dead	40	8.5	27.6	25.0	4.75	26.5	1.73	11.7	13.4	39.7

* Roentgen therapy given in terminal phase; period after nitrogen mustard was uneffective is not included as it was rarely effective in this group.

Lymphosarcoma. Previous reports have commented on the variability in the response of the lymphosarcoma to nitrogen mustard.[10–13] Our group of ten cases illustrates this well. (Table II.) Case 65, a fifty-five year old male, has been in remission five years since his first course of nitrogen mustard. Two cases with advanced disease have had active recurrences two to three months following each course but there has been a gradual decrease in the activity of their disease over a three-year period. Each patient has now had a remission without any evidence of disease for eighteen to twenty-four months since the last course. A significant remission was not obtained in another patient (Case 58) despite rapid resolution of lymph node masses. A response which may be designated as satisfactory (*good* or *fair*) was obtained in seven cases. (Table V.) One-half of the cases with lymphosarcoma were in poor condition at the beginning of nitrogen mustard therapy and six are now two patients who did not respond to chemotherapy. This predominantly good response represents an average duration of disease to date of 47 months; in the four patients who died it is 41.5 months and 51.3 months in the six living patients.

Chronic Lymphatic Leukemia. Ten cases of chronic lymphatic leukemia have been observed following nitrogen mustard therapy. As in the lymphosarcoma group, the response has varied considerably, being relatively poor in advanced or very active disease and good in cases which had not yet developed anemia. The single remissions in this group varied from zero to nineteen months, an average of 4.4 months. Our average period of observation in the group was 16.3 months with four patients still living. Eight patients were in advanced stages of disease with anemia and splenomegaly when treatment was started. Only two of these showed a good response. The two relatively early cases responded well

with prolonged remissions, with normal health and freedom from lymphadenopathy or anemia.

Giant Follicular Lymphoma and Follicular Lymphoblastoma. One patient with giant follicular lymphoma (Brill-Symmers) was observed and treated early in the disease. This patient has received four courses of nitrogen mustard with remissions averaging 4.6 months. There have been spontaneous fluctuations of lymphadenopathy during the period between courses of therapy but we have seen little progression of the disease. In the past twenty-four months we have, therefore, observed this patient without therapy.

Five cases were classified as follicular lymphoblastoma to denote anaplastic invasive character. (Table IV.) Each was in the fifth or sixth decade of life and had a history of lymphadenopathy several years prior to diagnosis. We have observed these individuals only in the later invasive stage of their disease. Nitrogen mustard therapy produced resolution of the lymph gland masses for short periods but no prolonged clinical remission resulted. In three of the cases considerable relief from pain was achieved for three to four weeks. The variability in behavior of this lymphoma is so great that no estimate can be made of the influence nitrogen mustard may play in controlling the disease from its onset. It is clear, however, that when lymphoblastomatous degeneration has occurred only brief palliation can be expected.

TABLE IV

RESULTS IN GIANT FOLLICULAR LYMPHOMA AND FOLLICULAR LYMPHOBLASTOMA

Case No.	Unit No.	Sex	Age	Probable Onset	X-ray Effect	No. of Courses	Average Dose (mg.)	Total Remission	Present Status
Benign Giant Follicular Lymphoma									
78	319150	M	38	7/43	None	4	22	46.5	Lymphadenopathy
Follicular Lymphoblastoma									
79	415679	F	43	3/46	14 mo.	1	30	1	Dead/2 mo.
80	406570	F	54	3/42	6 mo.	1	27	1	Dead/3 mo.
81	418649	M	43	1941	2 mo.	1	22	1	Dead/5 mo.
82	411609	M	64	1944	None	1	30	1	Dead/4 mo.
83	46611	F	64	1942	.....	1	20	3 mo.	Invalid P^{32}

TABLE V

RESULTS OF NITROGEN MUSTARD THERAPY IN LYMPHOMAS AND LEUKEMIAS (CLASSIFIED ACCORDING TO SCHEDULES OF TABLE I)

Disease	Total	Failure	Poor	Fair	Good	Living	Dead
		(No. of Cases)					
Hodgkin's granuloma	40	2	9	9	20	16	24
Hodgkin's sarcoma	17	8	8	1	0	1	17
All Hodgkin's	57	10	17	10	20	17	41
Lymphosarcoma	10	1	2	3	4	6	4
Chronic lymphatic leukemia	10	4	2	2	2	4	6

OBSERVATIONS

It is apparent that nitrogen mustard therapy will ameliorate the clinical manifestations of the lymphomas in a large proportion of cases. In arriving at a clinical evaluation of nitrogen mustard therapy several questions remain to be considered:

(1) Does the information at hand suggest preferential use of nitrogen mustard in the control of specific symptoms? (2) What is the proper relationship of nitrogen mustard to irradiation therapy? (3) Does nitrogen mustard therapy offer a longer useful life expectancy to the patient with a lymphoma?

Clinical Response to Nitrogen Mustard. Prior reports of this group and others[10–13,16] have commented on the response of various clinical symptoms to nitrogen mustard therapy. Lymphadenopathy developed in all the patients at some period in their disease. Completeness of resolution varied from moderate softening and reduction in size to reduction to the extent that the nodes were not palpable. The degree of resolution correlated well with the stage of the disease, being greatest in the early granulomas and least satisfactory in the extensive sarcomas. The same characteristic response was seen in the various infiltrated areas as the mediastinum, the liver, spleen and peripheral lung field. The latter has the same ominous significance described by the radiotherapists.[18] The reaction of the febrile phase of either the Pel-Ebstein or septic type to nitrogen mustard is of some prognostic interest since lysis of fever either occurred within ninety-six hours of treatment or was incomplete and not followed by a clinical remission. We have not been impressed with the response of bone lesions. In five patients (Cases 9, 12, 32, 36 and 37) of this group with osteolytic lesions, pain was relieved for some weeks by this treatment but there was no radiographic evidence of recalcification. Wintrobe et al.[19] report encouraging evidence of healing in several of their patients.

Three patients suffered severe pruritus and many had mild pruritic episodes with exacerbation. The latter usually responded to treatment; however, only two patients experiencing severe pruritus with lichenification and excoriations healed promptly. Pruritus is alleviated if the other manifestations of the disease are controlled by nitrogen mustard therapy.

It is obvious that in the use of nitrogen mustard one should be concerned about the reaction of the hemopoietic system and its ability to regenerate (a total of 470 mg. has been given to one patient, Case 28). The blood picture in this group has been followed carefully but there is no evidence that the material has a cumulative effect or that anemia becomes a more prominent factor because of this form of therapy. Indeed, we are more impressed with the regeneration of hemoglobin in the second month following therapy than by the moderate fall which occurs in the first month following treatment. The degree of anemia seen in this group is not greater than that observed following x-ray therapy to patients of comparable clinical status.

We have previously stressed the importance of considering nitrogen mustard only as a means of controlling systemic symptoms and relying on the use of local irradiation for the abolition of local areas of activity.[14,20] Nitrogen mustard is the treatment of choice when fever with toxic leukopenia, anemia or acute symptoms of pressure in chest or abdomen are the predominant features. In these cases the prompt response to chemotherapy without secondary edema is a marked advantage. From the clinical as well as pathologic approach it is better to give nitrogen mustard before irradiation since there is evidence that the cells are less sensitive to nitrogen mustard after irradiation.[21]

Relationship of Nitrogen Mustard to Irradiation Therapy. The most efficacious use of nitrogen mustard therapy may be determined by comparison of the response to chemotherapy alone, when used as an adjunct to irradiation, and following the development of roentgen resistance. One of the most useful features of nitrogen mustard therapy has been its effectiveness in alleviating the advanced disease which has been classified as roentgen-resistant. Of the forty patients who died twenty-six were so designated. (Table VI.) We have been impressed by the wide variation in the technic of irradiation and the criteria of resistance used by various observers. Although difficult, a careful classification of

the patients has been made in order to compare the course of the disease when irradiation is carried to the stage of resistance with that observed when nitrogen mustard therapy is begun before this resistant phase appears.

In Hodgkin's granulomas twenty-four cases were equally divided between the resistant and roentgen-responsive groups. In the former irradiation was given over a period of twenty-six months but in the responsive cases it was discontinued at thirteen months. The duration of the disease prior to chemotherapy was 25.5 and 30 months in the responsive and resistant cases, respectively. However, the period of effective nitrogen mustard therapy was approximately the same in both groups, 15.3 months in the responsive and 14.3 months in the roentgen-resistant. The extended period of control of the disease by irradiation is reflected in the total duration of the disease, since those considered x-ray-resistant survived 44.6 months or 3.8 months longer than the responsive group. The cases in the Hodgkin's sarcoma group were predominantly resistant to irradiation when nitrogen mustard therapy was started but there was no significant difference in the period of irradiation or survival of the two groups. The effective period of nitrogen mustard therapy and the total duration of disease is approximately ten months less in this group than in the granulomas.

For the evaluation of Hodgkin's disease as a single group, there are fourteen responsive cases and twenty-six cases in the resistant group. The duration of the disease at the time chemotherapy was begun was similar in the two groups, twenty-six and twenty-eight months, but irradiation had been carried out three months longer or over a period of fifteen months in the resistant group. The response of the latter group to nitrogen mustard was 9.3 months, or four months less than the group in which irradiation was interrupted (13.5 months). This short period of effective nitrogen mustard therapy is a reflection of the poor results in the sarcoma group. The total duration of disease is 38.5 months in the x-ray-resistant group and 35.4 months in the cases responding to irradiation when nitrogen mustard was started.

TABLE VI

COMPARISON OF THE RESULTS OF NITROGEN MUSTARD THERAPY IN ROENTGEN-RESPONSIVE AND NON-RESPONSIVE CASES

	No. of Cases (Dead)	First Symptoms to Treatment	Duration of Irradiation Therapy	Duration Prior to Nitrogen Mustard	Period of Effective Nitrogen Mustard Therapy	Total Duration
		(Time in Months)				
Hodgkin's granuloma	*24*					
Responsive	12	7.3	13.0	25.5	15.3	40.8
Non-responsive	12	8.0	26.0	30.0	14.3	44.6
Hodgkin's sarcoma	*16*					
Responsive	2	4.5	13.0	23.5	3.0	35.0
Non-responsive	14	10.8	13.0	25.4	5.0	33.2
All Hodgkin's cases	*40*					
Responsive	14	6.8	12.3	26.0	13.5	35.4
Non-responsive	26	9.5	15.1	27.3	9.3	38.5

Eighteen responsive cases; eight or 44 per cent living; average duration 72.5 months.
Thirty non-responsive cases; four or 13 per cent living; average duration 72.6 months.
Nine no irradiation cases; five or 55 per cent living; average duration 51.0 months.

Our data suggest that since the period of effective nitrogen mustard therapy is similar in the responsive and resistant group, it would be wise to continue irradiation to the stage of resistance. This does not exclude nitrogen mustard therapy early in the disease, for we believe clinical observations support the advisability of its use in attempting to control the many systemic foci of disease. We are now approaching the disease on this basis.

TABLE VII
COMPARISON OF DURATION FROM ONSET TO DEATH WHEN TREATED WITH IRRADIATION ALONE AND WITH NITROGEN MUSTARD—HODGKIN'S GRANULOMA

Duration (yr.)	Irradiation Plus Nitrogen Mustard (Present Group) (24 cases)	Irradiation Alone	
		Jackson and Parker (136 cases)	Uddströmer (494 cases)
	Per cent	Per cent	Per cent
1	8	24	33
1–2	33	45	45
3–4	38	17	16
5–9	17	13	6
10	4	1	0

The five year survival in this group is 45.7 per cent.
The average duration of disease among the living cases is 62.0 months.

Nitrogen Mustard Therapy Alone. There are nine patients in this group who have been treated only with nitrogen mustard. Four of these patients died after 23.3 months of disease during which nitrogen mustard was effective in controlling the disease for 8.1 months. Among the five that continue under observation nitrogen mustard has been effective nineteen months, and the duration of the disease to date is fifty-one months. While this group is small and all cases had advanced disease when therapy was started, it does not seem likely that chemotherapy alone will prove as effective as irradiation.

Survival under Various Types of Therapy. The possible increase in survival produced by the combination of irradiation and nitrogen mustard in Hodgkin's disease is of most interest in this study. In our group of Hodgkin's granuloma twenty-four patients died. This survival rate may be compared with that of three earlier reports.

TABLE VIII
COMPARISON OF SURVIVAL IN HODGKIN'S DISEASE IN REPRESENTATIVE TYPES OF TREATMENT

	Treatment	Five-year Survival (Per cent)	Average Duration (mo.)
Minot and Isaacs (1926)	None	12	19
Nathanson and Welch (1937)	Irradiation	23	30
Medinger and Craver (1942)	Spray irradiation	32*	44
Present group (1948)	Nitrogen mustard	30†	40

* 16 per cent of cases were terminal when therapy was begun.
† 50 per cent of cases were terminal when therapy was begun.

Uddströmer[22] and Jackson and Parker[17] have tabulated the survival distribution of their cases on an annual basis. (Table VII.) Our granulomas have a three-year survival of 59 per cent as compared with 22 per cent and 31 per cent in the other series. The average survival of this group is 42 months, which is similar to that attained by Gilbert[18] using x-ray therapy.

A comparison of survival in Hodgkin's disease under varying circumstances of care is tabulated on Table VIII. These groups include survival without treatment, with local irradiation, spray irradiation and nitrogen mustard with local irradiation. It is noted that the five-year survival without treatment is but 12 per cent and the average duration 19 months.[23] Local irradiation increased the survival to 23 per cent and the average duration to 30 months in the group of Nathanson and Welch.[24] This compares favorably with the reports of others using this type of therapy,[25,26] and to the series of Hamann[27] collected in the same clinic in which our work was performed. Slaughter and Craver[28] have reported an average survival of 24 months from onset of therapy using local irradiation. The average case in this group had symptoms seven months prior to therapy. Using the Heublein spray irradiation technic, Medinger and Craver[29] have attained an average

duration of 44 months and a five-year survival of 32 per cent. This is slightly better than the results in the present group which show a five-year survival of 30 per cent and an average duration of 40 months. Thus, nitrogen mustard produces a significant improvement over local therapy and may represent an improvement over the Heublein technic, since Craver's series included a constant number (16 per cent) of cases in an advanced stage of disease while our group included 50 per cent with advanced disease. In addition to the forty patients mentioned above, seventeen are living and have responded to nitrogen mustard twenty-two months, with an average duration of disease to date of 65 months.

Lymphosarcoma. The wide variation in the results of therapy in lymphosarcoma may reflect the variable criteria used in classifying lymphosarcoma. We have included in this group only those tumors composed primarily of small lymphocytes. Craver et al.[28,29] attained an average survival of 12.4 months with local therapy and 24.2 months with the spray technic. This is significantly less than the survival of 41.5 months in our six patients who died. This may be the result of limited experience but it is supported by careful tissue classification to avoid the inclusion of other lymphomas which commonly are placed in this group. We believe that careful continued observation in this group of diseases is indicated.

Chronic Lymphatic Leukemia. We have remarked upon the variable response of chronic lymphatic leukemia to nitrogen mustard therapy. It is clear that the small lymphocytic type, which is usually slowly progressive and frequently exhibits lymphadenopathy, limited splenomegaly and moderate anemia, will respond well and have a longer period of normal health. The more active types, with larger lymphocytes and advanced disease, usually did not have remissions of more than one month. Wintrobe[19] concurs in this experience.

Follicular Lymphoblastoma. We have described five cases of follicular lymphoblastoma, which are active tumors and sensitive to nitrogen mustard but are not amenable to therapy because of their rapid, invasive growth. There is reason to believe that this may be a terminal phase of a less malignant tumor. Our experience with nitrogen mustard, and that of Meyer[30] and others using irradiation, indicate the poor prognosis in this group.

Miscellaneous. Our first report on nitrogen mustard therapy[11] included cases of chronic myeloid leukemia, acute leukemia, reticulum cell sarcoma, multiple myeloma and sympathicoblastoma. With the exception of the last disease we have seen no significant remissions in this group. Some workers[19] have produced satisfactory remission in early chronic myeloid leukemia; however, we have studied only six cases of advanced disease. In this group and in the acute leukemias we have explored a variety of dose schedules but have not been impressed by their efficacy. Our experience with two cases of reticulum cell sarcoma has been unsatisfactory.

COMMENT

It is clear that nitrogen mustard therapy is useful in prolonging the social and economic life of patients with lymphomas, particularly Hodgkin's disease, and in giving palliative relief to many in their terminal phase. A longer period of observation is needed to define the best method of using this drug but present evidence indicates that it is not wise to exclude roentgen therapy. Most of the patients in this group have had x-irradiation prior to nitrogen mustard and in a few an effort was made to continue irradiation to local masses and use nitrogen mustard to control the multicentric foci of disease. In several advanced cases x-irradiation of large areas following nitrogen mustard therapy resulted in severe toxic reactions with anemia, leukopenia and purpura.[31] We believe, however, that future therapy should include relatively heavy local roentgen therapy to active foci and nitrogen mustard therapy, in the standard dose, at two- to three-month intervals to restrict multicentric foci at an early stage.

This is a practical means of handling the early regional case and may avoid dissemination for a relatively long period (Case 28). We do not believe that it is justifiable to defer chemotherapy if x-ray is not restricting the disease, or to defer irradiation of a local area of tumor in the absence of subjective symptoms.

Cautious adjustment of dosage is necessary in initiating therapy in cases with leukopenia. An excellent therapeutic result may be obtained in those patients with a toxic or hypersplenic depression of hemopoiesis. However, in cases with extensive myelophthisis, especially in lymphosarcoma and acute or chronic leukemia, late toxic manifestations may develop which may be aggravated by nitrogen mustard or roentgen therapy. In this situation we have frequently used courses of two or three standard doses, or reduced the daily dose to 0.05 mg. per kg. until the sensitivity of the individual patient to the drug was known. This has been a successful means of bringing several advanced cases to a state which permitted further nitrogen mustard or roentgen therapy, with repeated prolonged remissions (Case 34).

In each terminal case a phase developed in which there was widespread active growth of tumor, showing evidence of resolution after each course of treatment but recurring so rapidly that further treatment was considered inadvisable. This situation may be deferred even longer if a compound with more prolonged chemical action and greater selective tumor cytotoxic effect is found. As yet no congener of nitrogen mustard has shown more promise than the methyl bis β-chloroethyl amine.

SUMMARY

The clinical course of ninety-five cases of lymphomas and leukemias following therapy with methyl bis β-chloroethyl amine hydrochloride has been reviewed. These included fifty-seven cases of Hodgkin's disease, ten cases each of lymphosarcoma and chronic lymphatic leukemia, five cases of follicular lymphoblastoma, six cases of chronic myeloid leukemia and nine cases of other related diseases.

The response of each case is classified according to criteria based on the period of amelioration of symptoms and duration of effective nitrogen mustard therapy. The clinical improvement and marked palliation in cases, even those responding only briefly, indicates the value of this method of therapy in Hodgkin's disease, lymphosarcoma and chronic lymphatic leukemia.

The survival of forty patients with Hodgkin's disease averaged 40 months with a response to nitrogen mustard of twelve months. The seventeen patients still alive have responded 22.4 months and have an average duration of 65 months. This compares well with the best results reported for x-ray therapy and is especially encouraging in view of the terminal status of 50 per cent of the patients at the onset of nitrogen mustard therapy.

Roentgen-resistant cases survived slightly longer but had a shorter response to nitrogen mustard than when irradiation was interrupted. Irradiation should be continued as long as feasible in controlling local tumor masses, with nitrogen mustard as adjunctive therapy in suppressing multicentric dissemination of the disease.

Nitrogen mustard cannot be recommended as the sole therapeutic agent in lymphomas. As a rule the patient who responds well to irradiation will also respond well to nitrogen mustard.

Toxic manifestations of nitrogen mustard therapy were of significance only in five terminal cases which developed anemia, leukopenia and purpura. However, these symptoms as the presenting toxic features of lymphoma prior to nitrogen mustard therapy were frequently controlled for considerable periods.

The response of lymphosarcoma and chronic lymphatic leukemia is of sufficient promise to suggest continued use of nitrogen mustard therapy in cases selected according to certain clinical features.

REFERENCES

1. Gilman, A. and Philips, F. S. The biological actions and therapeutic applications of the β-chloroethyl amines and sulfides. *Science*, 103: 409–415, 1946.
2. Barron, E. S. G., Bartlett, G. R. and Miller, Z. B. The effect of nitrogen mustard on enzymes and tissue metabolism. I. The effect on enzymes. *J. Exper. Med.*, 87: 489–501, 1948.
3. Barron, E. S. G., Bartlett, G. R., Miller, Z. B., Meyer, V. and Seegmiller, J. E. The effect of nitrogen mustard on enzymes and tissue metabolism. II. The effect on tissue metabolism. *J. Exper. Med.*, 87: 503–519, 1948.
4. Friedenwald, J. S., Buschke, W., Scholz, R. O. and Moses, S. C. Some effects of sulfur and nitrogen mustards on cell nuclei in mammalian cornea. Approaches to Tumor Chemotherapy, pp. 358–378. A.A.A.S., Lancaster, 1947.
5. Bodenstein, D. The effect of nitrogen mustard on proliferating embryonic tissues. *Cancer Research*, 7: 49, 1947.
6. Graef, K., Karnofsky, D. A., Jager, V. B., Krichesky, B. and Smith, H. W. Clinical and pathologic effects of nitrogen and sulfur mustards on laboratory animals. *Am. J. Path.*, 24: 1048, 1948.
7. Kindred, J. B. Histologic changes occurring in the hemopoietic organs of albino rats after single injections of 2-chloroethyl vesicants. *Arch. Path.*, 43: 253–295, 1947.
8. Karnofsky, D. Z., Graef, I. and Smith, H. W. Studies on the mechanism of action of the nitrogen and sulfur mustards in vivo. *Am. J. Path.*, 24: 275–291, 1948.
9. Rhoads, C. P. Present status of nitrogen mustards in the treatment of neoplastic disease. *J. A. M. A.*, 131: 656–658, 1946.
10. Goodman, L. S., Wintrobe, M. M., Dameshek, W., Goodman, M. J., Gilman, A. and McLennon, M. T. Nitrogen mustard therapy. *J. A. M. A.*, 132: 263–271, 1946.
11. Jacobson, L. O., Spurr, C. L., Barron, E. S. G., Smith, T. R., Lushbaugh, C. and Dick, C. F. Nitrogen therapy: studies on the effect of methyl bis β-chloroethyl amine hydrochloride on neoplastic diseases and allied disorders of the hemopoietic system. *J. A. M. A.*, 132: 263–271, 1946.
12. Karnofsky, D. A., Craver, L. F., Rhoads, C. P. and Ables, J. C. An evaluation of methyl bis β-chloroethyl) amine hydrochloride and tris (β-chloroethyl) amine hydrochloride (nitrogen mustards) in the treatment of lymphomas, leukemias and allied disorders. Approaches to Tumor Chemotherapy, pp. 319–337, A. A. A. S., Lancaster, 1947.
13. Wintrobe, M. M., Huguley, C. M., McLennon, M. T. and Lima P. de C. Nitrogen mustard as a therapeutic agent. *Ann. Int. Med.*, 27: 529–540, 1947.
14. Spurr, C. L., Jacobson, L. C., Smith, T. R. and Barron, E. S. G. The clinical application of methyl bis (β-chloroethyl) amine hydrochloride to the treatment of lymphomas and allied dyscrasias. Approaches to Tumor Chemotherapy, pp. 306–318. A. A. A. S., Lancaster, 1947.
15. Karnofsky, D. A. The nitrogen mustards and their applications in neoplastic disease. *New York State J. Med.*, 47: 992–993, 1947.
16. Zanes, R. P., Jr., Doan, C. A. and Hoster, H. A. Studies in Hodgkin's syndrome. *J. Lab. & Clin. Med.*, 33: 1002–1018, 1948.
17. Jackson, H. and Parker, F. Hodgkin's Disease and Allied Disorders. New York, 1947. Oxford University Press.
18. Gilbert, Rene. Radiotherapy in Hodgkin's disease (malignant granulomatosis). Anatomic and clinical foundations; governing principles; results. *Am. J. Roentgenol.*, 41: 193–241, 1939.
19. Wintrobe, M. M. and Huguley, C. M. Nitrogen mustard therapy for Hodgkin's disease lymphosarcoma, the leukemias and other disorders. *Cancer*, 1: 357–382, 1948.
20. Spurr, C. L., Smith, T. R. and Jacobson, L. O. Chemotherapy in human lymphomas, leukemias and allied disorders of the hemopoietic system. *Radiology*, 50: 387–394, 1948.
21. Karnofsky, D. A., Burchenal, J. H., Ormsbee, R. A., Gorman, I. and Rhoads, C. P. Experimental observations on the use of nitrogen mustard in the treatment of neoplastic disease. Approaches to Tumor Chemotherapy, pp. 293–305, A. A. A. S., Lancaster, 1947.
22. Uddström, M. On the Occurrence of Lymphogranulomatosis (Sternberg) in Sweden 1915–1931, and Some Considerations as to Its Relation to Tuberculosis. Pp. 226. Copenhagen, 1934. Lund.
23. Minot, G. R. and Isaacs, R. Lymphoblastoma (malignant lymphoma). *J. A. M. A.*, 86: 1185–1265, 1926.
24. Nathanson, I. and Welch, C. E. Life expectancy and incidence of malignant disease. *Am. J. Cancer*, 31: 598–608, 1937.
25. Goldman, L. B. and Victor, A. W. Hodgkin's disease. *New York State J. Med.*, 45: 1313–1318, 1945.
26. Burger, R. E. and Lehman, E. P. Hodgkin's disease: review of fifty-four cases. *Arch. Surg.*, 43: 839–851, 1941.
27. Hamann, A. External irradiation with roentgen rays and radium in the treatment of leukemias, lymphomas and allied disorders of the hemopoietic system. *Radiology*, 50: 378–386, 1948.
28. Slaughter, D. P. and Craver, L. F. Hodgkin's disease—five-year survival rates; value of early surgical treatment. Notes on four cases of long duration. *Am. J. Roentgenol.*, 47: 596–606, 1942.
29. Medinger, F. G. and Craver, L. F. Total body irradiation, with review of cases. *Am. J. Roentgenol.*, 48: 651–671, 1942.
30. Meyer, O. Follicular lymphoblastoma. A report of six cases. *Blood*, 3: 921–934, 1948.
31. Smith, T. R., Jacobson, L. O., Spurr, C. L., Allen, J. G. and Block, M. A coagulation defect produced by nitrogen mustard. *Science*, 107: 474, 1948.

Hypercalcemia in Osteolytic Metastatic Cancer of the Breast*

ALFRED J. SWYER, M.D., CAPT. JAMES S. BERGER, M.C.,† HAROLD M. GORDON, M.D. *and* DANIEL LASZLO, M.D.

New York, New York

THE occurrence of spontaneous hypercalcemia in patients with cancer of the breast with widespread osteolytic metastases has been known for a long time. However, its clinical significance has not been fully understood in the past. It is important to recognize the clinical manifestations of this complication and to differentiate it from other conditions. Hypercalcemia contributes considerably to the morbidity of these patients and when allowed to persist will result in their premature demise. When this condition is diagnosed in its early stage and treated properly, the patient will frequently regain relative comfort although the ultimate prognosis remains unaltered.

In 1923 Klemperer[1] reported a case of hypercalcemia in a patient suffering from osteolytic metastases secondary to breast cancer which he believed was due to parathyroid hyperplasia. Subsequent to this report numerous investigators described spontaneous hypercalcemia associated with osteolytic lesions.[2–8] The majority of these patients upon whom an autopsy was performed revealed no parathyroid hyperplasia.

A series of investigations is being carried out in this institution on some clinical and metabolic manifestations of primary and secondary bone tumors. Herrmann, Kirsten and Krakauer[9] reported on hypercalcemia induced by the administration of testosterone and stilbesterol administered to women suffering from advanced metastatic bone disease. The present report deals with the hypercalcemic syndrome occurring spontaneously in patients with carcinoma of the breast with bone metastases. Seventy-one patients with cancer of the breast with bone metastases were observed during one year; the hypercalcemic syndrome developed in ten patients or 14 per cent. This high incidence is indeed worthy of note. If one is allowed to generalize from this limited experience, every seventh patient with bone metastases from carcinoma of the breast may be expected to exhibit hypercalcemia during some phase of her illness. The signs and symptoms associated with hypercalcemia were similar in all cases although the entire picture was not always encountered. A triad consisting of gastrointestinal disturbances, mental changes and renal impairment was usually seen. Anorexia, nausea and vomiting became persistent and pernicious. Disturbances in sensorium were frequent, being manifested in incoherence, speech difficulty, apathy, lethargy and somnolence which sometimes led to stupor or coma. At times the respirations were labored and deep. The urinary output gradually decreased resulting in oliguria and the renal impairment was further demonstrated by increasing blood urea nitrogen values. Marked constipation, increasing bone pain and terminal hyperthermia were noted in several patients. When a drop in serum calcium level was effected, vomiting ceased, urinary output increased and the patient concomitantly

* From the Division of Neoplastic Diseases, Montefiore Hospital, New York, N. Y. This investigation was supported by a Grant from the American Cancer Society.

† Stationed at Fitzsimons General Hospital, Denver, Colo.

exhibited clinical improvement, better appetite and increased alimentation.

When the clinician is confronted with the signs and symptoms described above occurring in a patient with widespread osteolytic lesions, it is important that he consider the possibility of spontaneous hypercalcemia. Once this complication is thought of, differentiation from those conditions with which it can be easily confused, such as cerebral metastases, intestinal obstruction or uremia, can readily be made and proper therapy instituted.

If hypercalcemia is diagnosed, the possibility that the prior administration of vitamin D or of sex hormones to the patient may be etiologic factors should be investigated. High doses of vitamin D are known to induce hypercalcemia and renal calcinosis.[10] The induction of hypercalcemia by means of the sex hormones has already been mentioned.[9]

A few laboratory aids are important for diagnosis and treatment of the patient. The serum calcium determinations were done in duplicate using the Clark and Collip[11] modification of the Kramer-Tisdall method which gives normal values ranging from 9 to 11 mg. per cent. Hypercalcemia was diagnosed when the serum calcium level was 12 mg. per cent or higher. In the ten patients studied values ranged from 12.3 mg. per cent to 20 mg. per cent. Serum inorganic phosphorus and alkaline phosphatase values, determined by the methods of Fiske and Subbarow[12] and Bodansky,[13] respectively, were not consistently changed during the episodes of hypercalcemia. The blood urea nitrogen was elevated, ranging up to 51 mg. per cent. Renal function, as measured by the urea clearance, was consistently and severely impaired. The urine analysis in most of these patients was normal.

Therapy in these patients was directed toward bringing their excessively high calcium values down to normal limits. Believing that this can be most readily accomplished by increasing renal excretion of the cation, we attempted to bring about this result by forcing fluids. Moreover, the clinical syndrome of anorexia, nausea and vomiting, lethargy and listlessness usually resulted in a state of dehydration which would serve to decrease elimination. Accordingly, large amounts of fluid were given to these patients by the oral and intravenous routes. Shorr[14] has shown that sodium citrate facilitates the excretion of calcium by the kidneys and recommends administration by the intravenous route. Several of our patients were given sodium citrate infusions. Better hydration was not the sole factor concerned in the improvement of the patients' condition because instances were observed in which production of an adequate urinary output did not result in a diminution of the serum calcium value or in symptomatic improvement.

In order to prevent rises in serum calcium from exogenous sources all of these patients were put on low calcium diets. However, we did not attempt to interfere with intestinal absorption of the cation by such technics as encouraging the formation of insoluble calcium soaps or increasing intestinal motility. Further suggestions for the management of these patients will be discussed subsequently.

Response to treatment was not always dramatic but was frequently so. Such improvement was invariably associated with a drop in serum calcium levels to normal, a decrease in blood urea nitrogen and creatinine levels, a decrease in nausea and vomiting, and an increase in urinary output. This improvement lasted from one week to three months. In five instances the spontaneous hypercalcemia recurred once or more often up to three times. Each of these recurrences was similarly treated. However, the longer the spontaneous hypercalcemia persisted unrecognized or untreated, and the more often it recurred, the more resistant it became to treatment. Under these conditions the patient exhibited the clinical and chemical signs of severe renal impairment, became comatose and succumbed.

Postmortem examinations were performed in six cases. All these cases had certain features in common, such as widespread tumor

replacement of bone by osteolytic metastases, as well as almost universal involvement of soft tissues varying only in the number of areas involved. Three of the patients had fractures. These were located in the femur, ilium and ribs. All ten patients had clinical evidence of impaired renal function during periods of hypercalcemia and five of the six at postmortem examination showed urinary tract disorders. Three patients had pyelonephritis, two acute and one chronic, and two had hydronephrosis, one arising from ureteral metastases and the other from extra-ureteral pressure. In addition, four patients, all of whom had nephrocalcinosis, showed other ectopic areas of calcification. The renal calcium deposits were distributed in the convoluted and collecting tubules and the loops of Henle. One patient who was a hypertensive with retinal hemorrhages had many atrophic glomeruli in the kidneys. An adrenal gland in one patient contained an area of necrosis and calcification. The parathyroid glands were examined in five of the six patients and in microscopic and gross examination appeared to be normal. Four representative patients are described:

CASE REPORTS

CASE I. G. M., a forty-nine year old white married female, had a left radical mastectomy for cancer of the breast in 1945 and was given extensive postoperative radiation. One year later metastases were noted in the right pubic bone. In the course of the patient's illness numerous other metastases involving practically the entire osseous system were discovered. She was treated with radiation to the sites most affected. Testosterone was also administered intramuscularly. Four weeks prior to admission to our hospital she was completely bedridden because of pain which was only partially relieved by morphine. Two weeks prior to admission she complained of headaches, nausea and vomiting. On admission we found a slightly confused, lethargic, somnolent patient who had marked anemia. Bone marrow aspiration yielded nests of tumor cells in a hypoplastic marrow. She had hypertension with an average blood pressure of 180/110 but was not in cardiac failure. There was diffuse bony tenderness and roentgenograms revealed osseous metastases involving the pelvis, the cervical and lumbar spines, and the left femur. Urine showed a trace of protein. Specific gravity varied but little; her maximum concentration was 1.013. She continued to have nausea and vomited while in the hospital. Hypercalcemia was then suspected and a serum calcium determination done. Serum calcium was found to be 20 mg. per cent, blood urea nitrogen 50 mg. per cent, inorganic phosphorus 3.8 mg. per cent and the alkaline phosphatase 3.4 Bodansky units. (Fig. 1.) Urea clearance was 15 per cent and 20 per cent of the normal on two occasions. The patient was treated with intravenous infusions of glucose, her oral food and fluid intake was increased and she responded promptly. As can be seen from the graph the blood values of urea nitrogen and calcium dropped progressively and were normal by her sixteenth hospital day. Concomitantly, there was marked improvement in the mental attitude of the patient and in her appetite as well as a decrease in nausea and vomiting. The patient was able to sit up and was comfortable in a wheelchair. For about eighty days she remained well. Then the symptoms recurred. In this second phase serum calcium was elevated to 13.7 mg. per cent. In spite of the same rather intensive treatment the hypercalcemia persisted for about three weeks but it gradually subsided as did the clinical manifestations. She returned to her daily routine spending part of her time in a wheelchair. About a month later a pathologic fracture of the left femur occurred while the patient was being removed from the wheelchair to bed. This led to an acute decline and exitus six days later. Two days before her demise the serum calcium was elevated to 14.4 mg. per cent, phosphorus was 5.5 mg. per cent and blood urea nitrogen was 28 mg. per cent.

Autopsy of this patient showed metastatic anaplastic carcinoma of the breast which had spread to the heart, liver, adrenals, thyroid, lungs, pleura and osseous system including the sella turcica with invasion of the posterior lobe of the pituitary body. Scattered calcific deposits were seen in the convoluted tubules, loops of Henle and collecting ducts of the kidneys. There were frequent atrophic glomeruli present.

CASE II. R. S., a seventy year old white widowed female, had a four-year history of painless lump in the breast which was removed by simple mastectomy in 1946. One year later a pathologic fracture of the left humerus developed and the patient was treated with

2,000,000 units of vitamin D, given over a period of three weeks, terminating three months prior to her admission.

On admission to this hospital she was found to be a pale, obese, completely bedridden patient complaining of diffuse pain. Lymph node metastases were present in the left supraclavicular fossa. The left humerus and femur were fractured and on x-ray examination areas of osteolysis were seen involving the ribs, skull, pelvis, dorsal and lumbar spines, shoulder girdle and femur. The urine on repeated examination showed a diminished range of concentration and dilution. Protein and red blood cells were absent. Anemia was marked. The total serum proteins were within the normal range as well as the albumin and globulin ratio. Additional chemical data are illustrated in Figure 2. On admission the serum calcium was 14.0 mg. per cent, blood urea nitrogen 40 mg. per cent, phosphorus 4 mg. per cent, alkaline phosphatase 2.2 Bodansky units. The urea clearance was 15 per cent of normal. During this phase the patient vomited, was lethargic, somnolent, anorexic and nauseated. She showed remarkable improvement following continued infusion of glucose and water. Her mental state improved, she became alert and nausea and vomiting ceased. During this phase of improvement she was mobilized and her appetite increased. The figure illustrates the return of the blood urea nitrogen and calcium to almost normal values. About the fiftieth hospital day a second phase of mental and physical deterioration took place. On the fifty-eighth day the serum calcium reached a peak of 18.1 mg. per cent, blood urea nitrogen was 40 mg. per cent, creatinine 2.2 mg. per cent, phosphorus 5.3 mg. per cent and alkaline phosphatase 8.4 Bodansky units. The patient responded again to intravenous fluid administration. The critical manifestations subsided and the chemical data returned to nearly normal range. The renal status, however, as measured by the urea clearance, remained severely impaired. On the ninetieth hospital day a third phase of deterioration took place accompanied with elevation of the serum calcium to 13 mg. per cent. The patient died on the 118th hospital day.

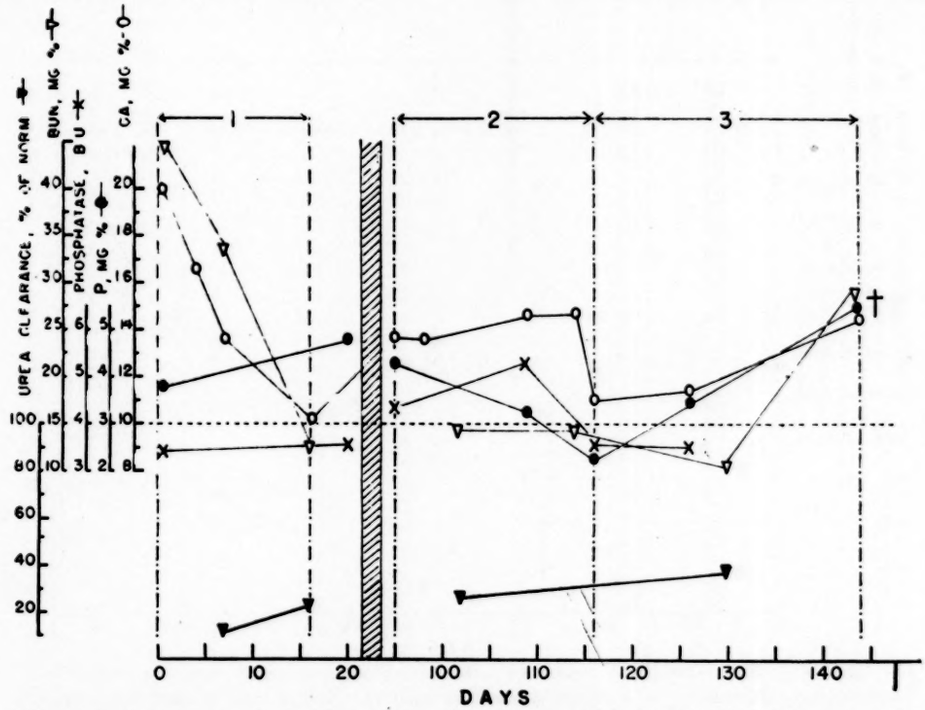


FIG. 1. Graph represents three hypercalcemic phases in patient G. M., forty-nine years old, with generalized osseous breast cancer metastases. The third hypercalcemic phase occurred a few days before her demise. The values of serum calcium, phosphorus, alkaline phosphatase, blood urea nitrogen and urea clearance in per cent of the normal, are indicated.

CASE III. L. P., a thirty-two year old white married female, had a right radical mastectomy performed in March, 1947, for carcinoma of the

breast. In October of the same year sudden low back pain radiating to both legs appeared. One month prior to admission she became completely bedridden. Two weeks prior to admission nausea and vomiting appeared and increased in severity.

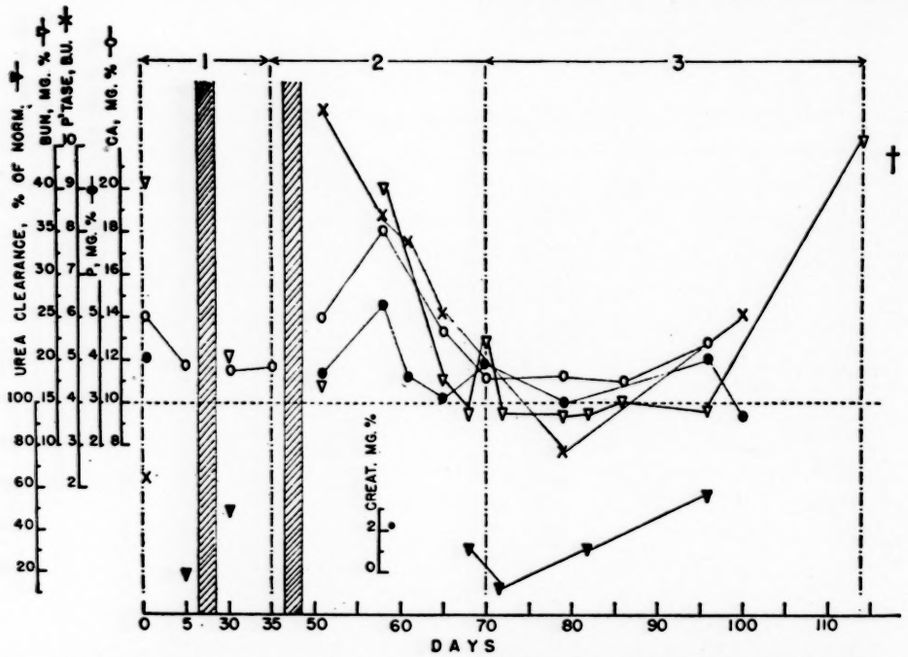


FIG. 2. Graph illustrates three hypercalcemic episodes, occurring during a period of four months' hospitalization, in a seventy year old patient (R. S.) with generalized osseous breast cancer metastases. Three months prior to her admission the patient completed a course of vitamin D medication. The reappearance of hypercalcemia in the second episode with a peak of 18 mg. per cent on her fifty-eighth hospital day indicates spontaneous hypercalcemia rather than that induced by vitamin D poisoning.

On admission the patient was cachectic, vomited persistently, had moderate anemia and was in pain. Urine was essentially normal except for a fairly fixed specific gravity.

Roentgenograms revealed evidence of osteolytic metastases involving the entire pelvis and lumbar spine with partial collapse of the body of the fourth lumbar vertebra. The chemical data obtained on this patient are illustrated in Figure 3. A week after admission the serum calcium was 12.3 mg. per cent, blood urea nitrogen was 48 mg. per cent and urea clearance was low. She was treated with intravenous administration of glucose solution and responded promptly. Sensorium cleared and serum calcium levels dropped to 10.3 mg. per cent. The period of improvement was brief and was followed by a second phase of rise in serum calcium and blood urea nitrogen and a return of nausea and vomiting. On her twenty-ninth hospital day the serum calcium reached a peak of 20.9 mg. per cent, then fell off gradually to 15 mg. per cent. Concomitantly, subjective improvement and decrease in nausea and vomiting were noted. On the fortieth hospital day progression of metastatic disease led to the development of jaundice, hepatomegaly and ascites. The serum calcium again rose to 18.3 mg. per cent, blood urea nitrogen to 35 mg. per cent. This time the patient failed to respond to supportive measures and died on her sixty-ninth hospital day.

Postmortem examination revealed metastatic carcinoma to the left breast, axillary and preaortic lymph nodes, lungs, liver, spleen, pancreas, vertebra, ilium, ribs and sternum. There was evidence of extramedullary hematopoiesis in the spleen. Both kidneys showed acute pyelitis and metastatic calcinosis.

CASE IV. R. B., a forty year old patient, was observed in this hospital for a period of one year. Her illness began in 1947 with pain in the right hip and increasing weakness. A tumor of the right breast was incidentally discovered. As extensive osteolytic metastases were already present, only partial right mastectomy and surgical castration were performed. Testosterone

therapy was instituted twice. On both occasions there was nausea and vomiting which forced its discontinuance. When admitted she was moribund, weighing 40 kg. and had severe anemia with a hemoglobin of 5.3 gm. and 1,900,000 red blood cells. X-rays showed diffuse osteolytic metastases to the cervical and lumbar spine, pelvis and ribs. Serum calcium was 9.6 mg. per cent, blood urea nitrogen 21 mg. per cent, alkaline phosphatase 3.1 Bodansky units and urea clearance 59 per cent of normal. The patient's general condition improved remarkably on transfusions, improved nutrition and discontinuance of morphine medication. Radiotherapy to the cervical spine and orthopedic support allowed this patient to ambulate freely and comfortably. This remission lasted for a period of six months when pain returned, again requiring increasing amounts of analgesics. Progression of the osteolytic metastases with signs of spinal cord damage were noted. Nausea and vomiting appeared and in this stage hypercalcemia was first noted. The serum calcium was 15.2 mg. per cent, the blood urea nitrogen was 18 mg. per cent and the urea clearance was 41 per cent of normal. These and the ensuing chemical data are illustrated. (Fig. 4.) The patient's intractable pain necessitated neurosurgical intervention, prefrontal lobotomy. The pain was only temporarily controlled by this measure and ever increasing doses of morphine were required. During this entire phase complete immobilization ensued because of the severe pain, paraparesis and extensive bone involvement. Nausea and vomiting, lack of fluid and food intake were present. The serum calcium remained persistently elevated. Attempts were made to increase the food and fluid intake and to improve the anemia. However, all these attempts failed. The urea clearance which was 59 per cent of normal in the phase of remission reached a low of 12 per cent on the 100th day of hypercalcemia. She died in uremia on the 125th day.

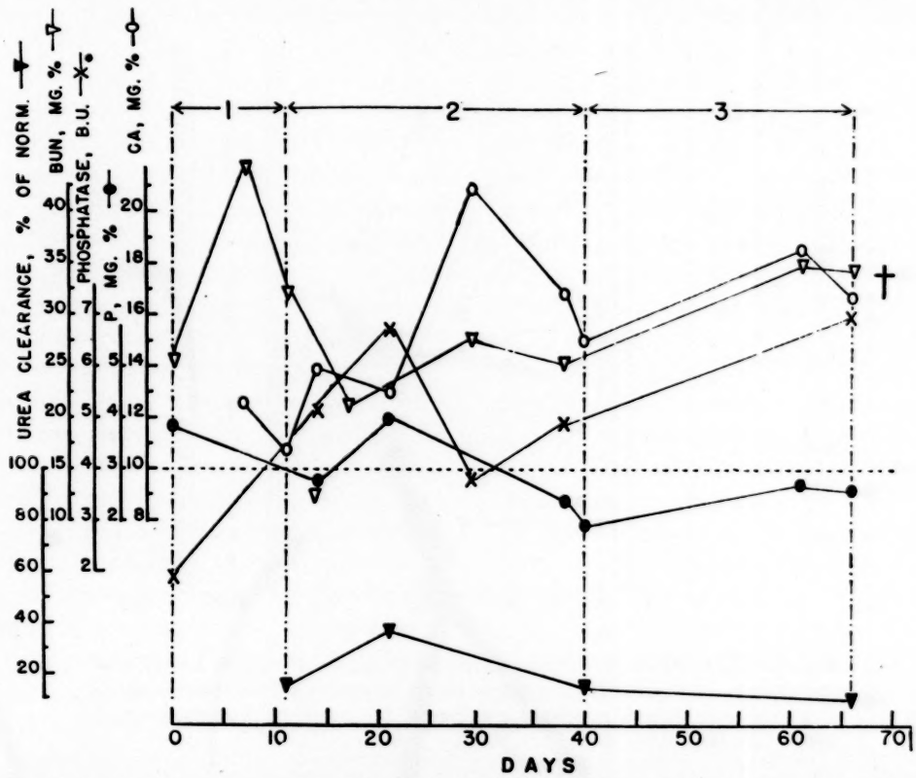


FIG. 3. Graph shows three hypercalcemic phases occurring in a thirty-two year old patient with breast cancer, L. P., with osteolytic bone metastases. Whereas the first calcium rise was minimal and lasted a few days only, the second and third peaks were considerably higher, the second responding but little to treatment; the third was refractory. The patient died in uremia.

At postmortem examination carcinoma of the right breast with metastases to the skull, dorsal

and lumbar spines, pelvis, ribs and shoulder girdles, liver, intracranial dura and pituitary were found. There was an acute pyelonephritis, also. Precipitated calcium spicules were seen within collecting tubules causing some destruction of the tubule walls.

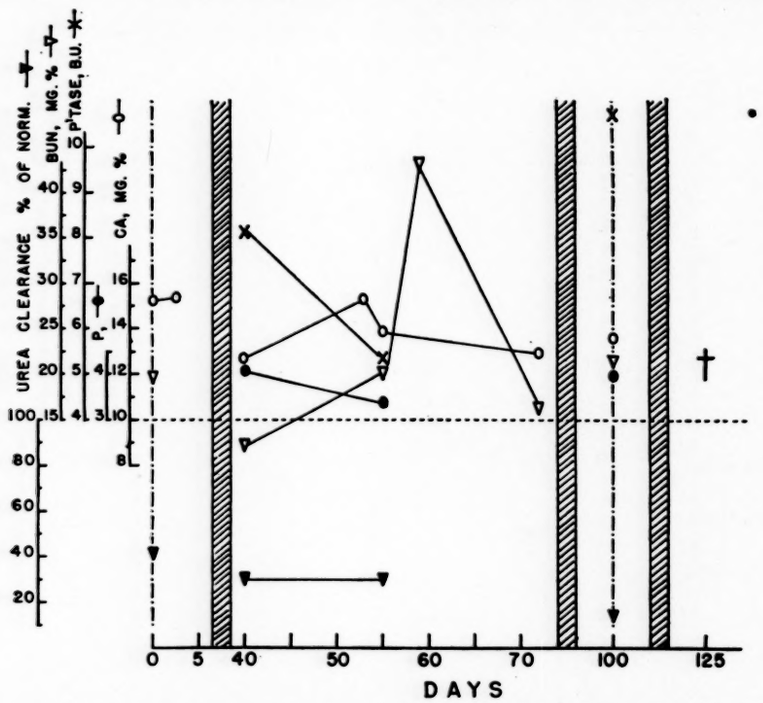


FIG. 4. Graph indicates a refractory phase of hypercalcemia in a forty year old patient, R. B., with osseous breast cancer metastases. The hypercalcemia developed in this patient after a long period of immobilization for multiple pathologic fractures.

COMMENTS

Osteolysis and hypercalcemia are associated with metastases of a variety of neoplasms. In addition to the metastases of neoplasm of the breast and multiple myeloma, these phenomena are associated with metastases from neoplasms originating in the kidney, bronchus, skin and central nervous system.[3]

Bone metastases secondary to breast cancer are predominantly osteolytic.[15] With widespread skeletal involvement and bone destruction an increased amount of calcium is made available for entry into the plasma. Gutman[3] believed that the resulting hypercalcemia is due mainly to the rapid demineralization. Egoville[4] postulated a systemic factor responsible for hypercalcemia which promotes the activity of skeletal metastates secondary to breast cancer. Farrow and Woodard[5] suggested a primary metabolic defect which may result in the transformation of sex hormones into sterols directly affecting calcium and phosphorus metabolism, thus rendering the bone more susceptible to metastatic invasion.

Immobilization *per se* is known to cause hypercalcemia in some instances, even in normal healthy individuals. Deitrick, Whedon and Shorr,[16] studying healthy male subjects, observed no osteoporosis but did find a negative calcium balance and a minimal but definite elevation of the serum calcium when the subjects were immobilized in plaster casts for a period of six weeks. Howard, Parson and Bigham[17] observed a greater urinary calcium excretion in immobilized individuals with fractures than was observed by Deitrick and his associates in immobilized normal subjects.[16] Albright, Burnett, Cope and Parson[18] reported a case of a fourteen year old boy in whom hypercalcemia, calcinuria and renal damage developed following immobilization for a

fracture. Upon ambulation normal calcium metabolism was restored. Several investigators described the occurrence of hypercalcemia in a series of children suffering from poliomyelitis.[19]

Many patients with advanced carcinoma of the breast and skeletal metastases are, in consequence, bedridden. If, in addition, pathologic fractures develop and orthopedic measures are applied, complete immobilization may result. Six of the ten patients reported here were nearly completely motionless at the time of the onset of hypercalcemia; four were at least partially ambulatory. Fractures, so frequent in this condition, probably accelerate the speed of rarefaction and thereby add to the deleterious effects of immobilization.

Renal insufficiency based upon previous organic disease may reduce the ability of the kidney to excrete calcium. This may not be apparent under conditions in which the kidney is presented with ordinary quantities of this cation. Even the normal kidney is unable to excrete calcium at times in sufficient quantity to prevent the establishment of hypercalcemia.[20] When excessive amounts of calcium reach the damaged kidney, it is unable to excrete the ion in sufficient quantities to prevent its accumulation in the serum. Hypercalcemia *per se* can produce further renal damage. Metastatic calcification varying from small precipitations in the tubules to large calculi in the renal pelvis are common results of hypercalcemia.

Nausea and vomiting are a common occurrence in hypercalcemic patients, resulting in further increase in plasma electrolytes. Oliguria follows with consequent calcium retention leading to further vomiting and dehydration and thus perpetuating a vicious cycle.

In discussing the problems of hypercalcemia consideration must be given to the role of the parathyroid gland. Indeed, anatomic parathyroid abnormality has been found to be associated with hypercalcemia occurring secondarily to metastatic bone tumors. Thus Klemperer[1] reported oxyphilic adenoma of the parathyroid and hypercalcemia in a case of generalized bone destruction resulting from cancer of the breast. Ben Ascher[21] reported a case of bronchogenic carcinoma with spontaneous hypercalcemia in which the parathyroids were thought to be responsible for the high calcium level persistent even after complete parathyroidectomy. The majority of cases of carcinoma of the breast with hypercalcemia reported by Loeper and Loeper[8] revealed no parathyroid hyperplasia. Mason and Warren[22] reported a case of metastatic carcinoma simulating hyperparathyroidism which failed to reveal parathyroid hyperplasia. Similarly, Albright and Reifenstein[23] reported a case of hypernephroma with solitary metastasis to bone with the chemical and metabolic findings of hyperparathyroidism, without anatomic evidence of parathyroid abnormalities. Interestingly, these chemical and metabolic abnormalities responded temporarily to radiotherapy of the bone metastasis. In none of our autopsy cases was morphologic evidence of parathyroid alteration found. From this review it is evident that hypercalcemia is only occasionally associated with anatomic abnormalities of the parathyroid gland. It is recognized that lack of anatomic lesions does not exclude the possibility of functional disturbance. Yet at present there is insufficient evidence to support this and only rarely are the metabolic findings characteristic of hyperparathyroid activity observed.

Several general measures are indicated in the management of cancer of the breast, with osteolytic metastases complicated by hypercalcemia. The food and fluid intake must be estimated; if inadequate, supplementation by tube feeding of mixtures enriched with proteins and/or parenteral fluid administration is indicated to maintain nutrition at its optimum. The judicious use of analgesics and hypnotics is advised. Ambulation is to be encouraged and aided by orthopedic appliances whenever necessary. That treatment of pathologic fractures should be selected which promises earliest ambulation. Bedside therapy, massage, active and passive exercise, have proven their value for bedridden patients. For those

patients who are immobilized the use of oscillating beds should help counteract demineralization.

SUMMARY

In a series of seventy-one patients with cancer of the breast with osteolytic metastases, spontaneous hypercalcemia was observed in ten, an incidence of 14 per cent. The characteristic clinical manifestations were the following, namely, mental changes, such as lassitude, lethargy, stupor and coma; gastrointestinal disturbances such as anorexia, nausea, vomiting and constipation, and renal insufficiency with oliguria, decreased renal clearance and retention of nitrogenous waste products in the blood.

The most important factor in the etiology of the hypercalcemia appears to be the dissolution of bone by metastases. However, prolonged bed rest, pathologic fractures and malnutrition due to anorexia and the side effects of pain-relieving drugs are important contributing factors. The overloading of the kidneys with calcium tends to maintain the hypercalcemia by causing renal calcinosis and thus may block this channel of compensation.

The importance of early recognition, differential diagnosis and treatment of the condition is stressed. The measures for the prevention and/or treatment of this condition consist of mobilization of patients whenever possible, aided by orthopedic procedures, oscillating beds, physical therapy, improved nutrition and fluid intake, as well as judicious selection and dosage of analgesic drugs. It is recognized that preventive or therapeutic measures do not change the ultimate prognosis for the patient but they may help to afford the patient a fairly comfortable life for a period of weeks or even months.

REFERENCES

1. KLEMPERER, P. Parathyroid hyperplasia and bone destruction in generalized carcinomatosis. *Surg., Gynec. & Obst.*, 36: 11, 1923.
2. ANDERSON, W. T. Some researches on calcium content of serum. *Hospitalstid*, 68: 1,177, 1925.
3. GUTMAN, A. B., TYSON, T. L. and GUTMAN, E. B. Serum calcium, inorganic phosphorus and phosphatase activity in hyperparathyroidism. *Arch. Int. Med.*, 57: 379, 1936.
4. EGOVILLE, J. W. Metastatic calcification in cancer. *Arch. Path*, 26: 1,047, 1928.
5. FARROW, J. H. and WOODARD, H. Q. The influence of androgenic and estrogenic substances upon the serum calcium. *J. A. M. A.*, 118: 339, 1942.
6. SCHWANDER, H. and MARVIN, H. N. Treatment of carcinoma of the human breast with testosterone propionate. *J. Clin. Endocrinol.*, 7: 423, 1947.
7. ADAIR, F. E. and HERRMANN, J. B. The use of testosterone propionate in the treatment of advanced carcinoma of the breast. *Ann. Surg.*, 123: 1,023, 1946.
8. LOEPER, J. and LOEPER, J. Hypercalcemia in the course of breast and prostatic cancers with bony metastases. *Progr. med.*, 74: 70, 1946.
9. HERRMANN, J. B., KIRSTEN, E. and KRAKAUER, J. S. Hypercalcemic syndrome associated with androgenic and estrogenic therapy. *J. Clin. Endocrinol.*, 9: 1, 1949.
10. DANOWSKI, T. S., WINKLER, A. W. and PETERS, J. B. Tissue calcification and renal failure produced by massive dose vitamin D therapy of arthritis. *Ann. Int. Med.*, 23: 22, 1945.
11. CLARK, E. P. and COLLIP, J. B. A study of the Tisdall method for the determination of blood serum calcium with a suggested modification. *J. Biol. Chem.*, 63: 461, 1925.
12. FISKE, C. H. and SUBBAROW, Y. The colorimetric determination of phosphorus. *J. Biol. Chem.*, 66: 375, 1925.
13. BODANSKY, A. Determination of plasma phosphatase. *Proc. Soc. Exper. Biol. & Med.*, 28: 760, 1931.
14. SHORR, E. Relationship between the excretion of citric acid and calcium. *Science*, 96: 587, 1942.
15. ACKERMAN, L. V. and DEL REGATO, J. A. Cancer, Its Diagnosis and Treatment. P. 940. St. Louis, 1947. C. V. Mosby Co.
16. DEITRICK, J., WHEDON, G. D. and SHORR, E. Effects of immobilization upon various metabolic and physiological functions of normal men. *Am. J. Med.*, 4: 3, 1948.
17. HOWARD, J. E., PARSON, W., BIGHAM, R. S., JR. Studies on patients convalescent from fracture. *Bull. Johns Hopkins Hosp.*, 77: 291, 1945.
18. ALBRIGHT, F., BURNETT, C. H., COPE, O. and PARSON, W. Acute atrophy of bone (osteoporosis) simulating hyperparathyroidism. *J. Clin. Endocrinol.*, 1: 711, 1941.
19. HOWARD, J. E. Hypercalcemia and renal injury. *Ann. Int. Med.*, 16: 176, 1942.
20. LEARNER, A. J. Calcium deposition in tissues of dogs and mice by the aid of parathormone. *J. Lab. & Clin. Med.*, 14: 921, 1929.
21. BEN-ASCHER, S. Metastatic bone carcinoma associated with parathyroid hyperplasia and symptoms of hyperparathyroidism with blood calcium and phosphorus studies before and after extirpation of the gland. *J. Lab. & Clin. Med.*, 24: 709, 1939.
22. MASON, R. L. and WARREN, S. Metastatic carcinoma simulating hyperparathyroidism. *Am. J. Path.*, 7: 415, 1931.
23. ALBRIGHT, F. and REIFENSTEIN, E. C., JR. The Parathyroid Glands and Metabolic Bone Disease. Baltimore, 1948. Williams & Wilkins Co.

Use of Paraffin-embedding Methods in the Cytologic Study of Various Bodily Secretions*

N. R. Bothereau, M.D.
Berkeley, California

The study of the cellular content of various bodily secretions, particularly vaginal, pulmonary and gastric secretions, has been developed and advanced to a considerable degree in the past few years. Such studies had been carried on for many years but it is only recently that these methods through improved technics have been widely and intensively applied. Papanicolaou and Traut[1] were among those who were particularly instrumental in the development of this field. The extensive studies which followed their pioneer work on vaginal smears and the widespread application of the method as an aid in the diagnosis of cancer are well known.

For many years pathologists have made so-called "buttons" from pleural and ascitic fluid. The method involves the embedding in paraffin of the solid particles or sediment after centrifugation, after which the paraffin block can be sectioned and the sections stained and mounted in the same way as ordinary biopsy material.

The paraffin-embedding method lends itself well to the study of vaginal, pulmonary, gastric and other secretions. The method is simple and the sections generally can be interpreted with ease and rapidity. An important feature of the paraffin-embedding method is the necessity for coagulation of the secretions so that the mucus with its entrapped cells and bits of tissue can be filtered out and concentrated into a form like a "button" which can then be handled like a piece of tissue. Picric acid, as was pointed out by Hunter and Richardson,[2] coagulates such material well and they found that it was satisfactory to fix material in ordinary 10 per cent formalin and later to add the picric acid for coagulation. Birge, McMullen and Davis[3] have recently described a method in which the thinner, more watery types of fluids or secretions may be centrifuged and the sediment mixed with fibrinogen and thrombin, then fixed and embedded.

METHOD

The following method has been found to be especially useful and to be particularly adaptable to the routine procedures of an ordinary pathology laboratory; this latter feature is important as it permits the "button," after the first few preliminary steps, to be handled along with other tissues through the routine paraffin-embedding and staining procedures. The fixing agent which has been found most satisfactory is Allen's fluid (PFA_3), which consists of the following:

	No. of Parts
Picric acid, saturated aqueous solution	75
Formalin, C. P.	15
Glacial acetic acid	10
Urea	1

This fluid is an excellent tissue-fixing agent and gives remarkably fine cytologic detail. Secretions are well coagulated and the material can remain in the fluid almost indefinitely and will remain in excellent condition. A large quantity is prepared at one time and small specimen bottles (4 ounces) are half filled. The stock solution is well stirred before the small bottles are filled so that some of the excess picric acid crystals will be in each specimen bottle. Specimens are collected as follows:

Gastric Specimens. A tube is introduced as for a gastric analysis and about 30 cc. of the fasting

* From the Division of Medicine, University of California Medical School, San Francisco, Calif.

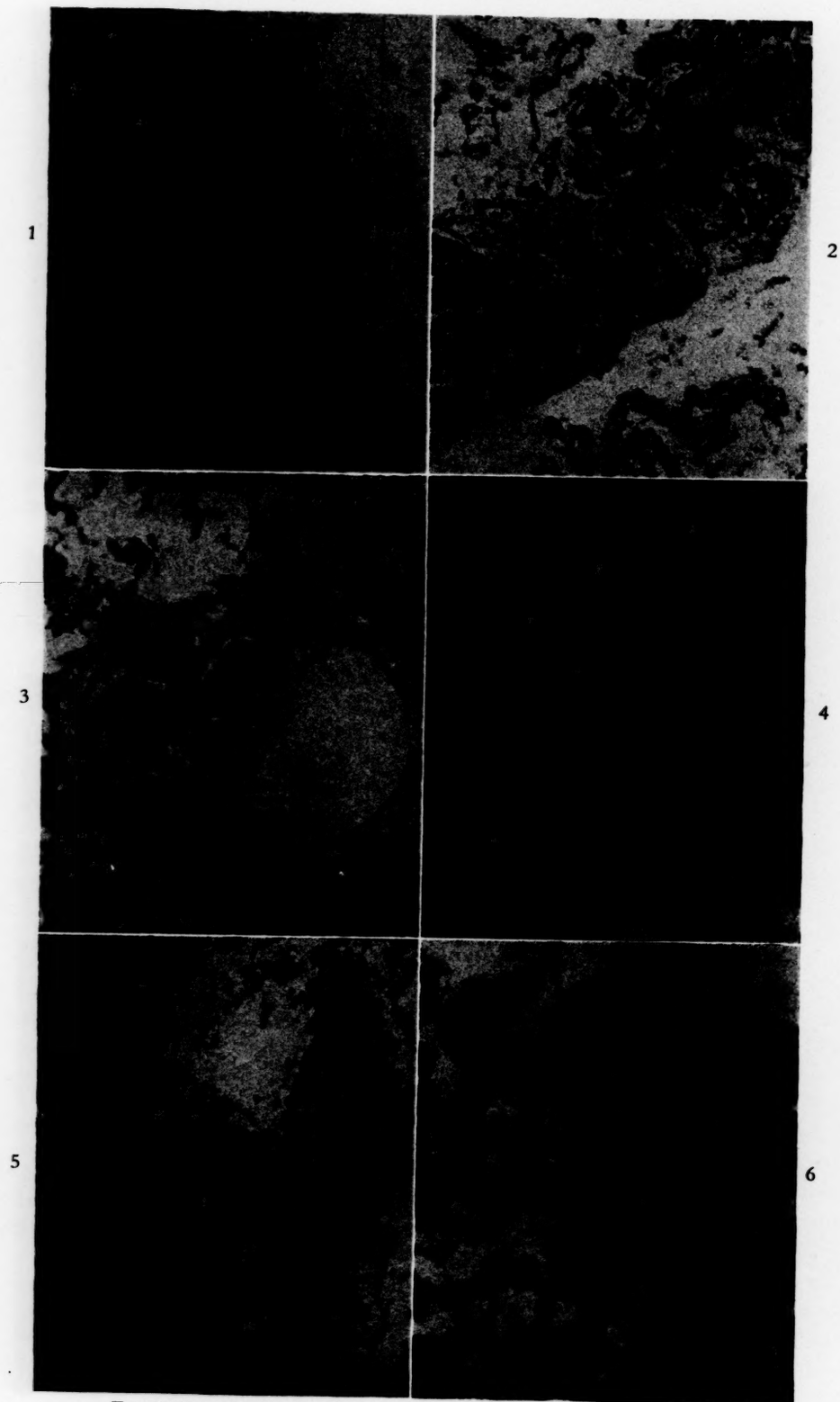


FIG. 1. Gastric washing showing relatively normal mucosa, × 100.
FIG. 2. Gastric washing; gastritis, × 100.
FIG. 3. Gastric washing; carcinoma, × 100.
FIG. 4. Same as Figure 3, higher power, × 960.
FIG. 5. Gastric washing; carcinoma, × 100.
FIG. 6. Gastric washing; carcinoma, × 960.

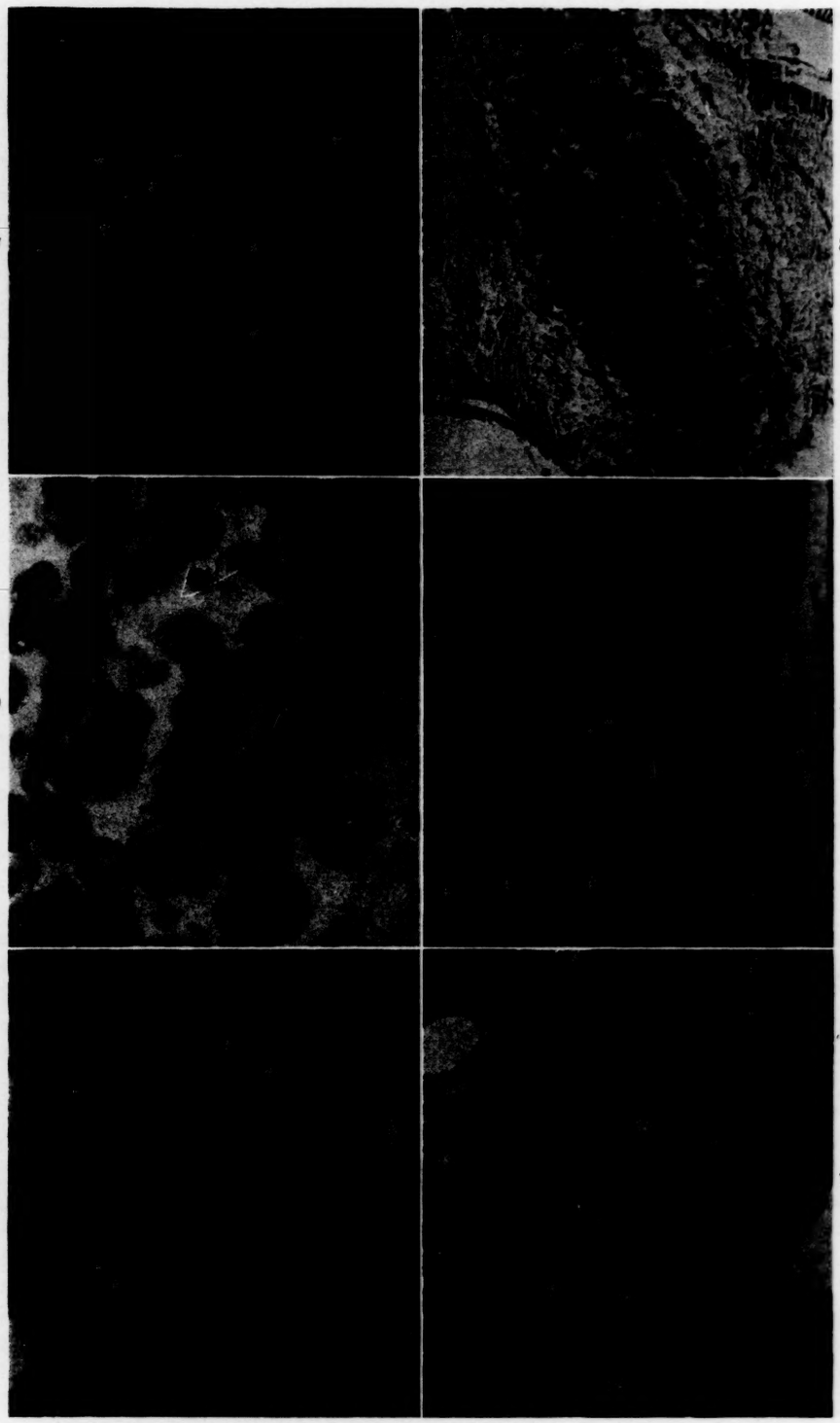


FIG. 7. Colonic washing; normal mucosa, × 100.
FIG. 8. Sputum; carcinoma, × 100.
FIG. 9. Sputum; carcinoma, × 960.
FIG. 10. Sputum; carcinoma, × 960.
FIG. 11. Sputum; carcinoma, × 960.
FIG. 12. Vaginal secretion; squamous cell carcinoma of cervix, × 100.

contents are aspirated and placed in a bottle of the fixing fluid. (Or, after a routine gastric analysis without, however, the use of crackers or other food, the tube is left in place and any residual material, usually only 5 to 20 cc., is aspirated and placed in a bottle of the fixing fluid.) Then, about 15 to 20 cc. of physiologic saline solution is introduced through the tube into the stomach and is washed back and forth several times. Usually some mucoid material is obtained. This aspirated material is added to the same bottle of fixing fluid. Occasionally there is a fairly large amount of watery secretion which may dilute the fixing fluid too much if an insufficient proportion of the latter is used. In general, it is best to use one to two parts of fixing fluid to one part of the secretions or washings. If the amount of watery secretion is large, the proportion of fixing fluid can be increased accordingly, or the secretion can be centrifuged a few minutes and a large part of the watery portion discarded, following which the remainder can be placed in the fixing fluid.

Duodenal Secretion. This is collected in a manner similar to that for gastric secretions. A double-lumen gastroduodenal tube is especially useful so that the duodenal contents can be kept entirely separate from the gastric. Studies are under way at present in which secretin is injected intravenously while the duodenal tube is in place to stimulate the flow of pancreatic secretion.

Colonic Secretion. The patient is given a saline enema the night before and on the following morning is given repeated irrigations with physiologic saline solution until the water is clear or free from fecal material. Then washings are obtained as with gastric specimens.

Sputum. It is essential that the sputum not stand more than an hour before it is placed in the fixing fluid. The most satisfactory method is to have the patient cough directly into the fixing fluid. Many patients cough only or chiefly in the morning on arising. These are given a bottle of the fixing fluid to take home and are instructed to cough into it.

Bronchial Secretion Obtained at Bronchoscopy. A small trap with about 1 cc. of the fixing fluid in it is attached to the instrument and the material aspirated into it. The contents of the trap are then transferred to a bottle of the fixing fluid. Specimens from different portions of the tracheobronchial tree can be kept separate, as may be indicated.

Vaginal Secretions. These are collected by means of an aspirating syringe and placed directly into the fixing fluid.

Further Steps in the General Procedure. In general it is best to leave the material in the fixing fluid from twelve to twenty-four hours. It is then filtered through coarse filter paper. The filtration time can be shortened materially by using a funnel inserted in a rubber stopper fitted into a flask with a side arm which can be connected to a suction device such as a water faucet having an aspiration connection. At times filtration is best done through lens paper, a large (4 by 6 inch) sheet of which can be fitted satisfactorily into a funnel. Filtration is generally more rapid through lens paper but later the solid material should be transferred to rough filter paper as the latter is more easily handled in the subsequent steps. After the superfluous fluid has been filtered out, the filter paper is lifted out of the funnel and carefully opened out. With a tongue blade the solid material is gently scraped together into a small mass. All of the surrounding filter paper, except for a margin of about ¼ to ½ inch around the mass, is clipped away. The mass is then wrapped in the remaining paper so as to hold it together, and a few turns of thread are placed around the package, but not tied, just sufficiently to keep it together. The package, which usually measures from about 0.5 to 2.0 cc. in volume for average specimens, is then placed in 50 per cent ethyl alcohol, using the same bottle which originally contained the specimen. At times, especially with certain specimens of sputum, it is not necessary to wrap the material; coagulation is so firm that the specimen can be handled almost as easily as a piece of solid tissue.

If facilities permit, the material after fixation can be centrifuged instead of filtered and the sediment transferred directly to a small piece of the coarse filter paper and wrapped as previously described. After one-half to one hour in 50 per cent ethyl alcohol the strength is increased to 60 per cent for from one-half to one hour, then to 70 per cent. The picric acid will color the alcohol yellow, but this is of no importance, and the material will continue to have a yellow color until it is stained. The material should remain in the 70 per cent alcohol two to four hours.

It is often well at this point to open the little package for it will be found that the mucus has been largely dehydrated, leaving the more solid

material spread about to some extent. With a tongue blade the material can again be gently and carefully gathered into a small compact mass and the package rewrapped.

It must be emphasized that in all of these procedures meticulous care is needed to insure that specimens are kept entirely separate and are uncontaminated by any material from other specimens which are being processed at the same time.

After the specimen has been in 70 per cent ethyl alcohol for the period previously mentioned it is ready for the routine procedures carried out in any pathology laboratory. It can be placed into the 70 per cent or 80 per cent alcohol container of a Technicon, for instance, and handled just as any biopsy specimen. In general it is best to leave on the filter-paper wrapping until the specimen is in the melted paraffin; the wrapping can be removed when the specimen is placed in the final paraffin in which it is blocked.

Specimens prepared in the foregoing manner can be sectioned very easily. A thickness of 6 micra has been found particularly satisfactory for the sections. Several sections from different parts of the block can be placed on one slide, thereby giving a greater degree of sampling.

Staining with ordinary hematoxylin and eosin, as is done with routine tissues, has given excellent results. The other steps, i.e., dehydration and mounting, are carried out as with routine tissues. In fact, these specimens in all but their early stages of processing are handled along with the routine biopsy and surgical specimens through the same solutions and procedures.

Thus it is apparent that except for the use of a special fixing agent (Allen's fluid), the filtering and wrapping procedure and the gradual dehydration up to 70 per cent alcohol, such specimens can be handled in the same way that ordinary pieces of tissue are handled. This is important for it means that the average pathology laboratory can easily include the specimens in its routine procedures. After the specimen has been collected and placed in the fixing fluid it can be turned over to the pathology laboratory where all of the steps described can readily be carried out. Or, the physician or the assistant collecting the specimen may find it possible in some instances to carry out the initial procedures up to the 70 per cent alcohol, at which point the pathology laboratory can take over. In either case the entire procedure is simple and rapid and has given very satisfactory results.

The paraffin sections afford an excellent means of studying intact bits of tissue in gastric, pulmonary and other material and may often be of the highest diagnostic importance. The sections, in general, are easily and rapidly interpreted. When, for example, substantial pieces of a gastric or pulmonary carcinoma are found, the diagnosis is as certain as when a positive biopsy is obtained. The accompanying photomicrographs illustrate some of the findings which have been obtained in sections of various types of material. (Figs. 1 to 12.)

Physicians can easily make available to themselves the simple procedures which have been described. These methods afford an added diagnostic tool approaching the direct biopsy in importance. Indeed, in those instances in which a biopsy is impossible paraffin sections of secretions or washings may be of the greatest diagnostic importance.

SUMMARY

1. The cytologic study, by means of paraffin-embedding technics, of various bodily secretions with special reference to gastric, duodenal, colonic and pulmonary material is discussed.

2. A simple technic is described which makes it possible to handle such material in much the same way that routine biopsy material is handled.

3. The application of the method to diagnostic problems, especially the diagnosis of cancer, is discussed and illustrated.

REFERENCES

1. Papanicolaou, G. N. and Traut, H. F. The diagnostic value of vaginal smears in carcinoma of the uterus. *Am. J. Obst. & Gynec.*, 42: 193–206, 1941.
2. Hunter, W. C. and Richardson, H. L. Cytologic recognition of cancer in exfoliated material from various sources. *Surg., Gynec. & Obst.*, 85: 275–280, 1947.
3. Birge, R. F., McMullen, T. and Davis, S. K. A rapid method for paraffin section study of exfoliated neoplastic cells in bodily fluids. *Am. J. Clin. Path.*, 18: 754, 1948.

Arthro-onychodysplasia*

Hereditary Syndrome Involving Deformity of Head of Radius, Absence of Patellas, Posterior Iliac Spurs, Dystrophy of Finger Nails

A. M. BRIXEY, JR., M.D. *and* RICHARD M. BURKE, M.D.
Joliet, Illinois *Oklahoma City, Oklahoma*

It is the purpose of this report to describe two members of a family exhibiting an hereditary syndrome consisting of (1) deformity and luxation of the head of the radius, (2) hypoplasia or complete absence of the patellas, (3) posterior iliac spurs and (4) dystrophy of the finger nails.

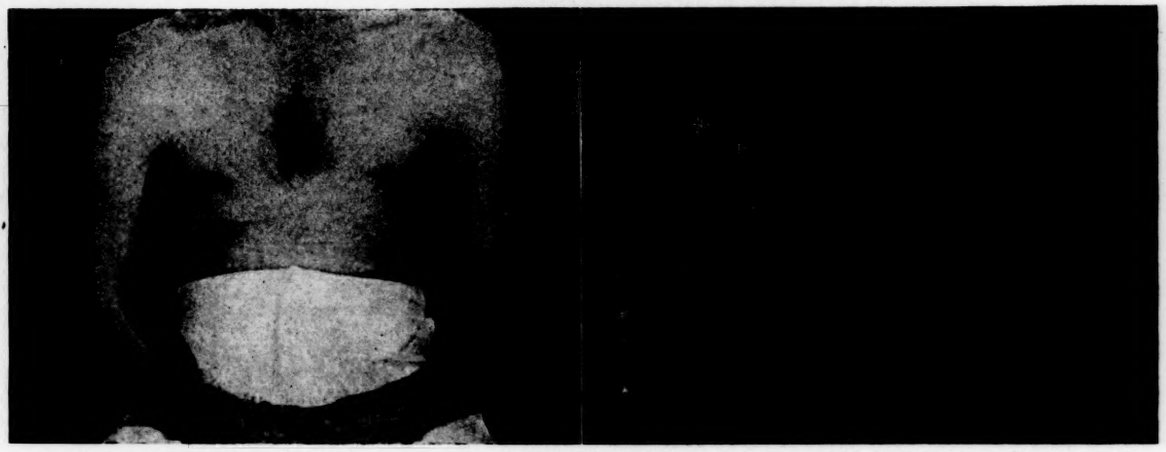
Hereditary transmission of congenital deformities of various systems has been described in some detail in the literature. These reports have been concerned primarily with defects in systems from the same embryologic cell layer. Instances of ectodermal origin are the frequent association of dystrophies of the nails, hair and teeth.[1–5] Of mesodermal origin are the examples reported by Snyder and Blank[6] of five family members with bridged sellas in three generations, and of eight families gathered from the literature by Aschner[7] in 1928 in whom a congenital defect or hypoplasia of the patella was inherited through several generations.

The occurrence of hereditary anomalies in tissues derived from more than one of the primordial germ cell layers is decidedly rare. Sedgwick[8] reported a family of four generations in whom eighteen members, mostly females, had neither patellas nor nails. Wolf's[9] report described a mother and two children with complete absence of patella and thumb nails. Rubin[10] described a family with small patellas and absence of thumb nails in three generations. Most[11] reported the absence of thumb nails along with anomalies of other nails and the absence of the patella, and Firth[12] described a mother and three children in whom there was congenital absence of the patella and deformity of the nails. Trauner and Rieger[13] wrote of a family of four generations in which six members had anomalies of the nails, luxation of the head of the radius and one member had hypoplasia of the patella.

Sever[14] tells of a man who was hospitalized for an inoperable carcinoma of the pancreas and was seen by him in consultation because of a knee deformity which produced some difficulty in walking. Examination showed a prominence of the internal condyle of the femur and a small patella which was displaced laterally forming a joint with the lateral surface of the external condyle of the femur on either side. The thumb nails were noted to be rudimentary bilaterally. In addition it was noted that there was some limitation of movement at the elbows where x-ray studies showed a bony overgrowth and exostoses. The genealogy could not be well worked out but others in the family (two of the patient's wife's nieces and a nephew, along with his mother's brother and niece) had been known to have similar nail changes—but in them nothing was known concerning the knee joints. This association of deformity of the nails and patellas has been reported with enough frequency to be called a definite hereditary syndrome by Aschner.[15]

To date there have been five reports in the literature of families in whom there was not only an inherited defect of the nails

* From the Department of Medicine of the University of Oklahoma School of Medicine, Oklahoma City, Okla.



1 2

FIG. 1. Case 1. Forearms held in complete extension; note webbing between the arm and forearm.
FIG. 2. Case 1. Dystrophy of both thumb nails with thinning of other fingernails.

and patellas but also of the head of the radius. Oesterreicher[16] described a family of five generations in whom eleven members were affected. In this series there was an anomaly of the patellas, femoral condyles, luxation and deformity of the head of the radius and atrophy of the thumb nails and less often an associated atrophy of the nail of the index finger. Turner[17] reported two family groups in whom there was an hereditary dystrophy of the nails, changes in the elbow with an increased carrying angle and inability to extend fully the forearms, rudimentary patellas, flaring of the ilium and small scapula. Lester[18] added a "clover leaf" deformity of pigmentation of the iris in reporting a family of three generations.

In Montant and Eggermann's[19] series a family of five generations displayed hypoplasia of the patella, malformation of the radius and hemiatrophy of the thumb nails, all found only in blue-eyed blondes. Senturia and Senturia[20] reported one case in a family which has had thirty affected members in the last four generations. The lesions included abnormalities of the patellas, nails and elbows.

CASE REPORTS

CASE 1. R. L. M., a white male, twenty-six years of age, was admitted to University Hospitals March 4, 1948, because of chronic nephritis in a terminal state with uremia and eventual coma, convulsions terminating in death on April 15, 1948. At the initial examination it was found that he had a webbing between the arm and forearm bilaterally (Fig. 1) with an increase in the carrying angle of the forearm, inability to extend the forearm completely (flexion was not impaired) and inability to perform the motions of pronation and supination. The head of the radius could be palpated as displaced posteriorly at the elbow. In addition there was dystrophy of the thumb nails and thinning of the other nails of the hands. (Fig. 2.) Palpation of the pelvic girdle revealed a bony protuberance which could be felt beneath the skin bilaterally below and posterior to the crest of the ilium. The anterior superior spine seemed prominent. Examination of the knees revealed an anterior flattening with a small patella lying laterally over the joint. The patella could be dislocated laterally on flexion of the knee. A mild bilateral equinovarus and a left indirect inguinal hernia were also present. No enlargement of the heart was detected. The blood pressure was 160/100 to 250/120.

The laboratory studies together with the clinical picture established a diagnosis of chronic nephritis with markedly diminished kidney function. An electrocardiogram was interpreted as showing suggestive evidence of low-grade left ventricular hypertrophy. X-ray studies showed a bony protuberance or "horn" extending posteriorly from each wing of the ilium. An elongation of the anterior superior spine was rather marked bilaterally (Fig. 3). Both elbows showed a very small capitellum of the humerus with malformation of the humeral condyles along with elongation of the neck and deformity

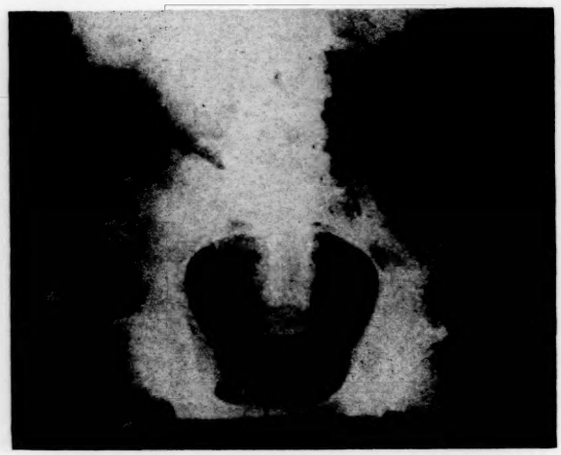


FIG. 3. Case I. Anteroposterior view of pelvis; note bony spur above and medial to the anterosuperior spine of the ilium bilaterally. There is also elongation of the anterosuperior spines.

and roughening of the head of the radius. There was also a posterior subluxation of the head of the radius most marked in the left elbow (Fig. 4). The patella measured 3 by 2½ by 1 cm. and was displaced laterally over the joint. There was slight flattening of the condyles of the femur. (Fig. 5.)

In addition to the aforementioned congenital deformities a left indirect inguinal hernia was noted at necropsy. With exception of the upper pole of each kidney, the tissue showed evidence of chronic glomerulonephritis by gross and microscopic examination. Slight cardiac hypertrophy, atheromatous change in the aorta and coronary arteries, and chronic and acute cystitis were also present.

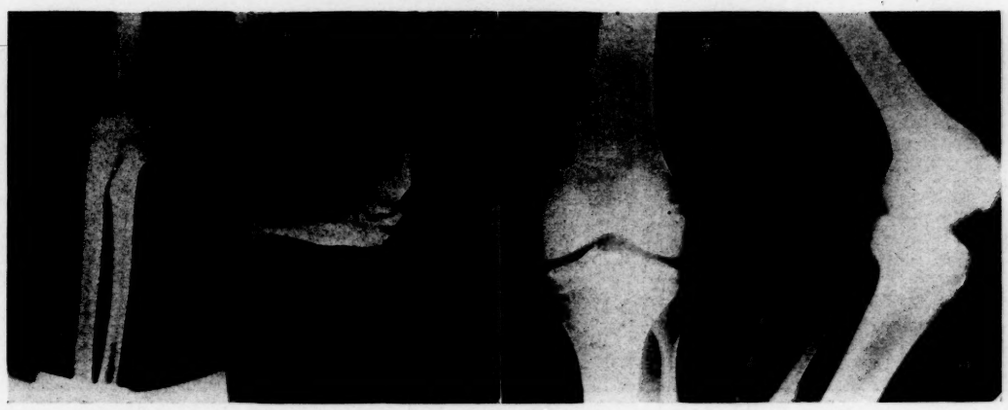
CASE II. L. L. M., a white female, forty-eight years of age, was the mother of the patient in Case I. She was brought in for pictures and x-ray studies when it was learned that she had similar deformities. She presented webbing of the elbows with inability to extend the forearms, along with limitation of pronation and supination. She had the trophic changes of the thumb nails, hypoplasia of the left patella and absence of the right patella, together with difficulty in walking and especially in descending stairs. Palpation of the pelvic girdle showed bony spurs extending posteriorly from the ilium which were much more prominent than in the case of her son.

Posterior iliac "horns" were present bilaterally, as shown in the x-rays. There was slight prominence of the anterior superior spines. There were marked hypertrophic changes of the lower lumbar spine, especially L_4 and L_5, with spurring, eburnation and roughening of the articular facets. (Fig. 6.) X-ray of the elbows showed that the capitellum was poorly formed and the radial heads had the same malformations as described previously, namely, a long neck and posterior subluxation (Fig. 7.) The right patella was absent. The femoral condyles were flattened and a tibial plateau was present. The left patella was very small and displaced laterally (Fig. 8.) (Lateral dislocation occurred with flexion of the knee.)

This patient further stated that of a total of sixteen members in five generations six have been affected with the syndrome. (Fig. 9.) Information concerning the first generation (I-1 and I-2), and one member of the fourth generation (IV-1), could not be obtained from those living relatives whose whereabouts were known to our patients. Two suspect cases (V-1 and V-2) are reputedly unaffected and five members of the family are entirely normal. Our patient (III-5, L. L. M.) is the only affected member known to be living. Cases II-1 and II-2 died of "old age" and IV-3 expired at the age of twenty-three following surgery for small bowel obstruction and no visceral anomalies were noted at the time of death in another hospital.

COMMENTS

A careful review of the literature shows a total of five reports of families in whom there has been a definite hereditary association of trophic changes of the nails, hypoplasia or absence of the patellas, along with deformity and luxation of the head of the radius. In only two of these was mention made of the pelvis. Turner[17] stated that some of his patients showed an increase in the normal concavity of the external surface of the ilium, which gave the crest the appearance of an outward flare of its posterior half. In Lester's patients[18] the pelvis was clinically normal but there was a deformity of the ilium "with an increase in the normal concavity on the external surface of the ilium, and the crest of the ilium seems to be increased posteriorly."



4 5

FIG. 4. Case I. Anteroposterior and lateral views of the elbow; the capitellum is small. The head of the radius is deformed and dislocated posteriorly.

FIG. 5. Case I. Anteroposterior and lateral views of the knee; the patella is small and in a lateral location over the lateral condyle of the femur.

6A 6B

FIG. 6. Case II. A, anteroposterior view of the pelvis showing bilateral posterior iliac spurs along with marked arthritic changes of the spine; B, lateral view showing the bony spur extending posteriorly from the body of the ilium.

Our two cases showed definite bony spurs or horns which protruded posteriorly from the body of either ilium. This deformity was found by Fong while reading routine x-ray urograms. Fong's report[21] contained a note by the editor of Radiology which stated that he had seen one similar case several years previously. No other anomalies were reported in these two cases; the published films, however, appear very nearly identical with the films of the pelvis in our two cases. We believe that this developmental peculiarity should be listed as a part of the syndrome. It is our impression that the subjects reported by Turner[17] and Lester[18] have the same type of posterior iliac spurs. Turner's published films appear quite similar to the ones presented by our patients.

Because of the lack of a suitable name, examples of the syndrome have been difficult to locate in the literature. For this reason and because the data appear to establish a definite clinical syndrome, a designation is desirable and that of arthro-onychodysplasia is suggested.

7 8

FIG. 7. Case II. Lateral view of both elbows; note the small capitellum of the humerus and the deformity and posterior displacement of the head of the radius.
FIG. 8. Case II. Lateral view of the knee joints; note the small patella on the left. There is flattening of the tibial plateau with complete absence of the right patella.

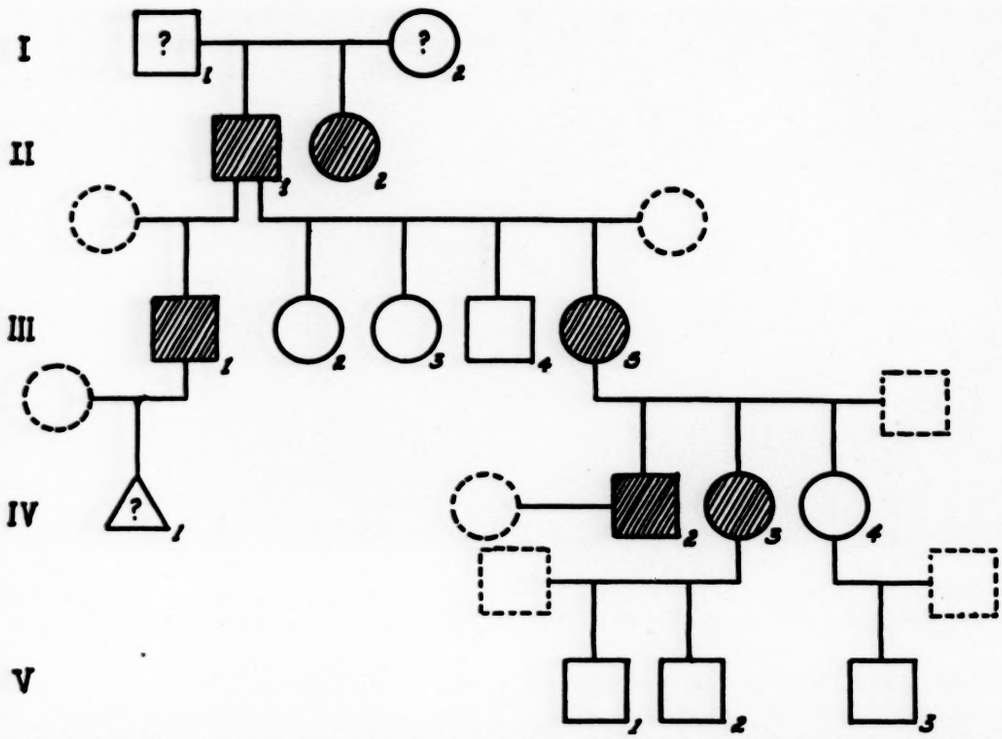


FIG. 9. Genealogy of the two cases of arthro-onychodysplasia (III-5 and IV-2) herein reported; the square figures represent males, the circles females. The affected members are indicated by cross hatching. Figures surrounded by broken lines are those who have joined the family by marriage. The sex and condition of IV-1, represented by the triangle, are unknown.

Hereditary Aspects. It is beyond the scope of this paper to present a definitive study of the genetics. Of interest, however, are several theories which have been advanced to explain the mechanism at work here.

Turner[17] in discussing his series of cases points out that in his first family all patients were affected in like manner (arthrodysplasia and dystrophy of the nails); whereas twenty-seven of forty-one members in the second family had dystrophy of the nails, only nine had an additional arthrodysplasia. Consequently, he argues that in the first family a single factor was responsible

for the inheritance of both ectodermal and mesodermal changes, whereas two factors were at work in the second family. Moreover, the factor for the nail dystrophy must be present for the factor for arthrodysplasia to be effective, since the bone changes were never found in the absence of the nail changes. As another possibility Turner suggested that there might be three factors involved, the third having a "repressive action on the factor for arthrodysplasia or on the interaction of the two."

Aschner[15] believed this to be an erroneous interpretation for two reasons, namely, that "first, one cannot assume essentially different laws for the representation of hereditary characters in the genotype (that is, the sum of all the potential hereditary factors present in the fertilized ovum) in different families." She states further that a phenotypic hereditary attribute which is represented once by only one gene and which is represented in another case by several genes in the same species is contrary to all hitherto known laws of experimental and human genetics. Secondly, she could not agree with Turner's hypothesis concerning the explanation of the hereditary occurrence of more than one anomaly. Aschner then offers her own explanation of these findings based on the beliefs of her mentor, Julius Bauer, that a close association of certain genes within the chromosome increases the probability of simultaneous pathologic mutation, because any damage of one, producing a change into its pathologic allelomorph, could easily involve its closest neighbors. Thus Aschner believes there is an individual gene for each of the observed anomalies and that these are linked together and very closely associated within the same chromosome.

A more plausible explanation can be found in the idea that a single gene is responsible for the multiple manifestations of the entire syndrome. This "pleiotropism" theory argues that a gene, in addition to its primary effect, has other additional and usually minor recognizable effects.[22–24] These effects may be produced by the action on the various anlage by the gene itself or they may be brought about by the action of a single gene which sets off a chain of reactions in the process of development ("spurious pleiotropism").[25] In the latter instance the earlier the action of the gene in question, the greater is its effect on the adult organism. As Dunn[26] points out there are certain "inducing" or "organizing areas" or centers within the very early embryo which act upon responding cells to bring about a regular sequential change. If one of these centers is inactivated by destruction or injury, there should follow an abnormal development of the parts dependent upon it, after which abnormalities could be produced with regularity. There are many apparent examples in animals described in the genetic literature. A syndrome of numerous anomalies in man which is thought to be produced in this fashion is that of acrocephalosyndactyly which, in addition to the dome-shaped skull and syndactylous hands and feet, often includes contractures, spina bifida, polydactyly, harelip and low intelligence.[26] Landauer[27] has suggested that there are genes which have a growth-inhibiting action at a certain period of life, whence a single gene could bring about a veritable chain of deformities.

The authors join Montant and Eggermann,[19] Trauner and Rieger[13] and Oestereicher[16] in their conviction that the arthro-onychodysplasia syndrome is brought about by a single gene mutation. Moreover, it is believed that the numerous manifestations are probably brought about by the action of the mutated gene in the early embryonic development of the young organism.

SUMMARY*

1. An hereditary syndrome consisting of (1) deformity and luxation of the head of the radius, (2) hypoplasia or complete absence of the patellas, (3) posterior iliac spurs

* Since the preparation of this paper, a report[28] of a single case of this syndrome has appeared. Apparently there were no other members of the family involved for there is no mention of it. The x-ray films show essentially the same anomalies as seen in the films presented in our cases.

and (4) dystrophy of the finger nails is discussed. The name arthro-onychodysplasia is suggested for this syndrome.

2. Two cases of arthro-onychodysplasia within the same family are reported.

3. Genetic factors in this syndrome are discussed.

Acknowledgment: The authors wish to express their thanks to Dr. Peter E. Russo for his interpretation of the x-ray films; to Drs. Paul R. David and Laurence H. Snyder for their suggestions concerning the genetic aspects of this syndrome and to Dr. Robert H. Bayley for his helpful advice and criticism.

REFERENCES

1. Tobias, N. Hereditary familial dystrophy of the nails. *J. A. M. A.*, 84: 1568, 1925.
2. Thompson, H. B. Hereditary dystrophy of the nails. *J. A. M. A.*, 91: 1547, 1928.
3. Jacobsen, A. W. Hereditary dystrophy of the hair and nails. *J. A. M. A.*, 90: 686, 1928.
4. Barrett, A. M. Hereditary occurrence of hypothyroidism with dystrophies of the nails and hair. *Arch. Neurol. & Psychiat.*, 2: 628, 1919.
5. Strandskov, H. H. Inheritance of absence of thumb nails. *J. Hered.*, 30: 53, 1939.
6. Snyder, L. H. and Blank, F. Studies in human inheritance. XXIV. Bridged sella as a genetic trait. *Ohio State M. J.*, 40: 318, 1944.
7. Aschner, B. Zur Erbbiologie des Skeletsystem. *Ztschr. f. Konstitutionslehre.*, 14: 129, 1928.
8. Sedgwick, W. Cited by Little, E. N. Congenital absence or delayed development of the patella. *Lancet*, 2: 781, 1897.
9. Wolf. Cited by Montant and Eggermann.[19]
10. Rubin, G. Congenital absence of patellae and other patellar anomalies in three members of same family. *J. A. M. A.*, 64: 2062, 1915.
11. Most, A. Ein Fall von kongenitalen Bildungsanomalien: Intrauterine Belastungsdeformitäten der unteren Extremitäten, Anonychie und Onychatrophie congenita. *Allg. med. Centr.-Ztg.*, 72: 153, 1903.
12. Firth, A. C. D. Congenital absence of patellae and deformity of nails in a mother and three children. *Proc. Roy. Soc. Med.*, 5: 44, 1912.
13. Trauner, R. and Rieger, H. Eine Familie mit 6 Fällen von Luxatio radii congenita mit übereinstimmenden Anomalien der Finger und Kniegelenke so wie der Nägelbildung in vier Generationen. *Arch. f. klin. Chir.*, 137: 659, 1925.
14. Sever, J. W. Hereditary Arthrodysplasia associated with dystrophy of the nails. *New England J. Med.*, 219: 87, 1938.
15. Aschner, B. A typical hereditary syndrome: dystrophy of the nails, congenital defect of the patella and congenital defect of the head of the radius. *J. A. M. A.*, 102: 2017, 1934.
16. Oesterreicher, W. Gemeinsame Vererbung von Anonychie beziehungsweise Onychatrophie, Patellardefekt und Luxatio radii. Dominantes Auftreten in 5 Generations. *Ztschr. f. Konstitutionslehre.*, 15: 465, 1930.
17. Turner, J. W. An hereditary arthrodysplasia associated with hereditary dystrophy of the nails. *J. A. M. A.*, 100: 882, 1933.
18. Lester, A. M. A familial dyschondroplasia associated with anonychia and other deformities. *Lancet*, 2: 1519, 1936.
19. Montant, R. and Eggermann, A. Syndrome héréditaire charactérisé par une hypoplasie des rotules, une malformation des radius et une hémiatrophie de l'ongle du pouce. *Presse méd.*, 45: 770, 1937.
20. Senturia, H. R. and Senturia, B. D. Congenital absence of the patellae associated with arthrodysplasia of the elbows and dystrophy of the nails. *Am. J. Roentgenol.*, 51: 352, 1944.
21. Fong, E. E. "Iliac horns" (Symmetrical bilateral central posterior iliac processes). *Radiology*, 47: 517, 1946.
22. Waddington, C. H. An Introduction to Modern Genetics. New York, 1939. The Macmillan Company.
23. Dobzhansky, T. Genetics and the Origin of Species. New York, 1941. Columbia University Press.
24. Goldschmidt, R. Physiological Genetics. New York, 1938. McGraw-Hill Book Company.
25. Grüneberg, H. An analysis of the "pleiotropic" effects of a new lethal mutation in the rat (*Mus norvegicus*). *Proc. Roy. Soc., London*, 125: 123, 1938.
26. Dunn, L. C. Heredity and development of early abnormalities in vertebrates. *Harvey Lect.*, 35: 135, 1940.
27. Landauer, W. Concerning the existence of genes with a specific effect upon one germ layer. *Proc. Sixth Int. Cong. Genetics*, 2: 115, 1932.
28. Mino, R. A., Mino, V. H. and Livingston, R. G. Osseous dysplasia and dystrophy of the nails. *Am. J. Roentgenol.*, 60: 633, 1948.

Review

The Thermal Coagulation Point of Blood Serum*

I. Method and Clinical Interpretation

GEORGE B. JERZY GLASS, M.D.
New York, New York

FOR two years there has been a growing interest in this country in the defective thermal coagulation of blood serum in relation to cancer detection. This has been reflected in the iodoacetate test of Huggins, Miller and Jensen[1–2] and in the heat coagulation test of Black, Kleiner and Bolker,[3] both proposed as serologic tests for cancer.

It seems timely to discuss the principle upon which the thermal coagulation of blood serum is based and its history, to describe another simple method for detection of defective thermal coagulation and to present results of the largest series yet available which includes 1,500 tests in 1,160 individuals.

Thermal coagulation of blood serum is a continuous physical process due to intramolecular hydration of serum proteins,[4] mainly of the albumin fraction. It is first evidenced by turbidity in the still fluid serum. At a later stage a loose jelly-like structure forms which exhibits thixotropy, i.e., it becomes liquid on stirring or shaking and resolidifies on standing. Finally, during the heating procedure a compact coagulum occurs which does not display thixotropy and is no longer shattered by shaking.

The minimal temperature necessary for the formation of a gel or coagulum in serum, the thermal gelification or thermal coagulation point, depends largely upon the duration of heating and the criteria employed to test the gel formed. Prolongation of heating time lowers these points but only to a critical level below which the state of dispersion of the serum does not change. Thermal gelification or thermal coagulation of serum occurs *en bloc* and must be distinguished from flocculation (also called coagulation) of some serum proteins heated in the presence of electrolytes, as exemplified by the Bauer[5] or Weltmann[6] serum flocculation tests.

Early studies of thermal coagulation of serum proteins were made by Halliburton in 1884 and 1886,[7] and Mellanby in 1906.[8] They found that various albumin fractions present in normal and pathologic sera showed different thermal coagulation points, the range of which was between 56° and 100°C. It is possible, however, in the light of modern fractionation technics[9] that these different albumin fractions were contaminated by various amounts of alpha- and beta-globulin, which would account for differences in thermal coagulation.

In 1909 Schade[10] studied the first stage of thermal coagulation, i.e., the turbidity developed on heating diluted sera to 80° and 100°C. He noted some differences under pathological conditions. These studies were repeated in 1923 by other authors[11] who found differences in turbidity values between sera of patients with gastric carcinoma and patients with pernicious anemia. In 1918 Belak[12] developed a method for the determination of the second stage of thermal coagulation, i.e., the initial gelification of

* From the Department of Medicine, The New York Medical College, Flower and Fifth Avenue Hospitals. New York, N. Y.

the serum. Muller[13] using this method in sixty cases found some insignificant increase in thermal gelification point in tuberculosis, Hodgkin's disease, arthritis, gastric ulcer, etc. Between 1922 and 1924 several authors[14–19] in a small series of cases studied thermal gelification of serum by means of Mayer's method.[15] They found an increase in thermal gelification point of blood serum in nephritis with edema, and in selected cases of heart disease, anemia, jaundice, diabetes and syphilis.

In 1936 and 1937 the present writer studied the thermal coagulation point by a new technic and utilized the final coagulation stage instead of the initial gelification as the end point of the reaction.[20] The test consisted in determining the minimal temperature which, if applied for one minute, suffices to coagulate blood serum to such an extent that the coagulum loses its thixotropy and the serum gel cannot be broken even by powerful shaking. Normally the difference between gelification and coagulation of serum does not exceed 1° or 2°C. but under pathologic conditions this difference was increased considerably. This indicated that changes in pathologic sera may be detected more easily if the final and not an intermediate phase of heat coagulation was determined.

Of the first 400 patients tested[20] 103 had cancer. It became evident that the sera of many patients suffering from cancer, and particularly those with a neoplasm involving the abdominal viscera, showed an increased thermal coagulation point. With this technic the normal point was 75° to 80°C. whereas in patients with cancer it was often 85° to 95°C. and higher. While this change in thermal coagulation was very obvious in patients with cancer, it was also found in many others, for example in pregnancy, nephrosis, cardiac failure and severe infection. Consequently the change in thermal coagulation was in no way specific for cancer. By correlating the thermal coagulation point with total serum proteins in each case it appeared that the mechanism underlying the alteration depended mainly upon quantitative and perhaps qualitative disturbances in serum albumins.[20] This was the first paper to formulate the principle of defective thermal coagulation of blood serum in cancer, the non-specificity of this principle and its presumptive mechanism.

In 1948 Black, Kleiner and Bolker[3] described a new heat coagulation test which determines only the first stage of thermal coagulation, i.e., the turbidity. Since it is performed on plasma and is largely dependent upon the fibrinogen content, it has only a distant relationship to tests performed on blood serum and dependent upon serum proteins only.

In 1949 Huggins, Miller and Jensen[1] described a new technic for determination of the thermal coagulation of blood serum. In their procedure heating was prolonged to thirty minutes, the serum was diluted to a protein content below 1.5 per cent and the smallest concentration of coagulable protein was determined. They also refined the detection of defective thermal coagulation by determining the iodoacetate index, i.e., the smallest concentration of an iodoacetate solution sufficient to prevent the coagulation of blood serum heated at 100°C. and evaluated in terms of its total protein content. Based on studies of 300 patients, including about 100 with neoplastic diseases, Huggins et al., rediscovered the principle of defective thermal coagulation in cancer. Huggins[2] advocated this test as a "simple though rough test for cancer," although he also noted that positive tests were found not only in cancer but also in active pulmonary tuberculosis and some massive infections. Huggins also concluded that the defective thermal coagulation of blood serum depended upon quantitative and qualitative disturbances in serum albumins.

The data submitted in this and the following parts of this paper are intended to prove useful for the proper interpretation of the clinical value of the principle of defective thermal coagulation of blood serum in disease. These inferences may have implications for evaluation of related tests based upon the same principle.

MATERIAL AND METHOD

The thermal coagulation point was determined in thirty healthy adult males, thirty healthy adult females and in 1,100 patients. Of these 400 were reported earlier.[20] The point was determined twice in 143 cases, three times in fifty-four and four to seven times in twenty-six patients. Ward patients were utilized to provide a diversity of diseases and the diagnosis was established by the usual clinical methods; many times these diagnoses were verified by biopsy, operation or necropsy.

In all 1,500 tests the thermal coagulation point, determined within 1°C., is the minimal temperature which suffices in one minute to coagulate serum to such extent that the coagulum does not break when subjected to standardized shaking. Cohesion of the shaken gel was tested by the addition of hypertonic salt solution to observe flotation of broken particles.[20]

For routine purposes the method can be simplified. Four water baths are set for 80°, 83°, 89° and 95°C. Each water bath is provided with a rack, a heating element, thermostatic control and an electric mixer. The bath should be large to prevent a fall of temperature when the rack and its test tubes are immersed. A thermometer graduated to 1°C. should be placed in each bath and its bulb near to and level with the serum in the immersed tubes. The removable racks should have many openings into which small (external diameter 3 inches by ⅜ inch) Pyrex tubes will fit snugly. The test tubes must be dry and of the same size. Other types of racks may be utilized with proper safeguards to prevent fall of temperature.

A 0.25 cc. sample of the serum to be examined is placed in each of two tubes in each rack; this requires a total of 2.0 cc. of serum. The remaining tubes are filled with other sera. Each rack is immersed in its own water bath for exactly one minute (stopwatch). Then one tube after another is placed in an electrical shaker and shaken perpendicularly to the long axis of the tube for ten seconds (250 strokes per minute). Shaking the entire rack limits the amplitude of strokes and is not recommended. If no shaker is available, forty strokes of about 10 inches in amplitude in ten seconds may be performed by hand.

Afterward 0.5 cc. of 15 per cent magnesium sulfate or sodium chloride is added cautiously along the side of the tube and the tube is moved gently to observe any fragmentation of the material and flotation of particles.

Serum remaining fluid or gelified serum which breaks more or less completely on shaking is designated "non-coagulated." If the serum coagulum remains compact after shaking and does not float to the surface when salt solution is added, it is coagulated. The duplicate must show the same characteristics.

TABLE I

DETERMINATION OF THERMAL COAGULATION POINT OF BLOOD SERUM BY SIMPLIFIED METHOD

Simplified Denomination of the Level of Thermal Coagulation	Thermal Coagulation Point °C.	Presence (+) or Absence (−) of Thermal Coagulation at the Temperature of:			
		80°C.	83°C.	89°C.	95°C.
Normal.....	75–80	+	+	+	+
1 plus increase.	81–83	−	+	+	+
2 plus increase.	84–89	−	−	+	+
3 plus increase.	90–95	−	−	−	+
4 plus increase.	over 95	−	−	−	−

Readings are made on the basis of Table I. Serum thermal coagulation points are classified as normal (thermal coagulation point 75°–80°C.), 1 plus (81°–83°C.), 2 plus (84–89°C.), 3 plus (90°–95°C.), and 4 plus (over 95°C.). When 4 plus, the serum will not coagulate at 100°C.

The blood should be obtained with a dry syringe to prevent hemolysis or dilution for they change the point considerably. Fasting specimens yield the most reliable data.

Modification of this technic yields values for normal and pathologic thermal coagulation points different from those reported here. The main sources of error are the use of a wet syringe or test tube, inexact timing, fall of temperature when immersing the test tubes, inexact equalization of temperature of bath around the test tubes, improper standardization of the amplitude and number of strokes in shaking procedure.

THERMAL COAGULATION POINT OF BLOOD SERUM IN VARIOUS DISEASES

The detailed data obtained in 1,500 tests on 1,160 individuals are listed in Table II. For simplification this table lists the data obtained as normal, 1, 2, 3 and 4 plus increased thermal coagulation points, although they were actually obtained with exactitude to 1°C. When several tests were

TABLE II

THERMAL COAGULATION POINT OF BLOOD SERUM IN 1,160 CASES

Diagnoses	No. of Cases	Thermal Coagulation Point of Blood Serum						
		Normal (75°–80°C.)	Increased 1 Plus (81°–83°C.)	Increased 2 Plus (84°–89°C.)	Increased 3 Plus (90°–95°C.)	Increased 4 Plus (over 95°C.)	Increased 2–4 Plus	
							No. of Cases	Percentage among Cases Examined
Normal Subjects (Total)	60	60	0	0	0	0	0	0
Normal Pregnancy (Total)	44	13	12	17	2	0	19	43.2
Early	11	5	3	2	1	0	3	27.3
Late	33	8	9	15	1	0	16	48.5
Malignant Tumors of (Total)	162	52	25	43	4	38	85	52.5
Breast	11	6	2	3	0	0	3	27.3
Skin, lip, tongue	14	10	1	2	0	1	3	21.4
Cervix, uterus	25	16	4	4	1	0	5	20.0
Lung	8	3	3	2	0	0	2	25.0
Bones, prostate, thyroid	19	6	1	9	1	2	12	63.1
Abdominal viscera	85	11	14	23	2	35	60	70.6
Successfully Removed Tumors (Total)	5	3	2	0	0	0	0	0
Non-neoplastic Diseases (Total)	889	391	206	134	22	136	292	32.9
Pyogenic processes (Total)	68	9	9	17	2	31	50	73.5
pulmonary abscess	13	0	0	7	1	5	13	100.0
pyothorax	11	4	2	1	0	4	5	45.5
phlegmon, peripheral gangrene	10	1	0	1	0	8	9	90.0
purulent peritonitis, periappendicular abscess, pyosalpinx	12	1	1	1	1	8	10	83.3
purulent mastitis	3	1	0	1	0	1	2	66.7
purulent otitis, parotitis	6	0	2	1	0	3	4	66.7
infected abortion	13	2	4	5	0	2	7	53.8
Severe infections (Total)	78	16	12	24	8	18	50	64.1
pneumonia	32	10	4	6	1	11	18	56.3
acute and subacute bacterial endocarditis	9	0	1	4	0	4	8	88.9
typhoid fever	4	1	1	2	0	0	2	50.0
acute malaria (tertian)	33	5	6	12	7	3	22	66.7
Rheumatic fever	12	1	5	4	1	1	6	50.0
Active pulmonary tuberculosis	79	25	31	7	2	14	23	29.1
Hodgkin's disease	13	5	0	0	2	6	8	61.5
Leukemia (lymphatic and myelogenous)	11	4	4	2	0	1	3	27.3
Complicated pregnancy (infection, hemorrhage)	14	0	0	2	0	12	14	100.0
Nephrosis, nephrotic stage of glomerulonephritis, lower nephron nephrosis, eclampsia	20	0	0	2	0	18	20	100.0
Congestive heart failure	69	12	12	27	4	14	45	65.2
Compensated cardiovascular diseases	64	47	15	2	0	0	2	3.1
Body burns, frostbite	7	0	0	3	0	4	7	100.0
Diseases of digestive organs (Total)	200	114	54	17	3	12	32	16.0
ulcerative colitis (severe)	4	0	0	0	0	4	4	100.0
pyloric stenosis (of long duration)	8	0	2	2	1	3	6	75.0
obstructive jaundice (of long duration)	11	0	0	4	2	5	11	100.0
gallstone disease, hepatitis, hepatocellular jaundice	63	35	23	5	0	0	5	7.9
gastroduodenal ulcer, gastritis, nervous indigestion	46	31	12	3	0	0	3	6.5
colitis, irritable colon	57	38	16	3	0	0	3	5.3
liver cirrhosis (early)	11	10	1	0	0	0	0	0
Inflammatory processes of various organs (Total)	106	60	26	18	0	2	20	18.9
arthritis (acute and chronic)	24	18	3	3	0	0	3	12.5
exudative pleurisy	13	7	3	1	0	2	3	23.1
glomerulonephritis	32	17	8	7	0	0	7	21.9
adnexitis, endometritis, etc	22	11	7	4	0	0	4	18.2
osteomyelitis	5	3	1	1	0	0	1	20.0
lymphadenitis	10	4	4	2	0	0	2	20.0
Miscellaneous diseases (Total)	148	98	38	9	0	3	12	8.1
anemias of various types	24	18	3	2	0	1	3	12.5
Graves' and Addison's disease	11	3	4	2	0	2	4	36.4
acute intoxications (iodine, acetic acid)	8	5	2	1	0	0	1	12.5
diabetes mellitus	14	9	4	1	0	0	1	7.1
bronchitis, emphysema, fibroids, asthma, renal stone disease, chronic sinusitis, fractures, dislocations, etc	91	63	25	3	0	0	3	3.3
Total	1160	519	245	194	28	174	396	34.1

made on the same patient, the highest value is tabulated. While an increase above 80°C. was considered abnormal, a one plus increase was obtained in so many minor illnesses that it was regarded as merely borderline. Increases 2–4 plus (84°C. and above) were considered definitely abnormal.

Malignant Tumors. The data are discussed in Part II of this paper.

Pyogenic Processes. In diverse pyogenic infections of the chest, abdomen and extremities (Table II) a 3–4 plus disturbance of thermal coagulation was noted, the incidence rising at times to 100 per cent.

Severe Infections. As shown by data listed in Table II the thermal coagulation was frequently abnormal in pneumonia, bacterial endocarditis, typhoid fever and rheumatic fever. The incidence of this abnormality ranged from 50 to 88 per cent of cases in this group of diseases.

Pulmonary Tuberculosis. The level of the thermal coagulation point depended upon the degree, extent and character of the lesion. A 1–2 plus increase was customary with manifest tuberculosis, while a 3–4 plus value was almost invariably associated with advanced and rapidly progressive forms.

Since defective thermal coagulation seemed to occur much later than disturbances in other labile serologic tests, such as sedimentation rate, it is more ominous in the evaluation of this disease.

Hodgkin's Disease and the Leukemias. In advanced stages thermal coagulation was always defective. In early stages frequently no changes were found.

TABLE III

SURVIVAL TIME OF 179 CASES FOLLOWED UP FOR ONE YEAR AFTER THERMAL COAGULATION TEST

	No. of Cases	Percentage of Cases with Survival Time Less Than:		
		3 Mo.	6 Mo.	1 Yr.
I. Carcinoma of abdominal viscera:				
(a) thermal coagulation point increased 2–3 plus	13	61.5	100.0	
(b) thermal coagulation point increased 4 plus	32	100.0		
II. Active pulmonary tuberculosis:				
(a) thermal coagulation point normal or increased 1 plus	41			24.4
(b) thermal coagulation point increased 2–3 plus	13		76.9	92.3
(c) thermal coagulation point increased 4 plus	14	93.0	100.0	
III. Cardiovascular disease with heart failure:				
(a) thermal coagulation point normal or increased 1 plus	30			20.0
(b) thermal coagulation point increased 2–3 plus	22		45.5	72.7
(c) thermal coagulation point increased 4 plus	14	78.6	100.0	

Pregnancy. In early normal pregnancy thermal coagulation often was normal but increases were not uncommon particularly near term. If infection or hemorrhage complicated the condition (infected, threatened or incomplete abortion, puerperal sepsis, premature separation of placenta, placenta previa, accretion of the placenta, extrauterine pregnancy), thermal coagulation was commonly altered.

Nephrosis, Eclampsia. Lipoid and lower nephron nephrosis (due to mercury or sulfonamide) and eclamptic kidney were constantly associated with marked disturbances of thermal coagulation. In nephrosis this feature was as regular as edema, proteinuria and hypoproteinemia (100 per cent of cases).

Congestive Heart Failure. Two-thirds of these cases showed altered thermal coagulation of blood serum, irrespective of the genesis of the failure. Usually highest values were found in patients with peripheral edema or transudate in a serous cavity.

Since thermal coagulation is unusual in

compensated cardiac disease, an increase in a cardiac patient may indicate failure in the absence of another explanation. (Fig. 1.)

Burns and Frostbite. When extensive, burns and frostbite were very frequently associated with altered thermal coagulation even in the absence of infection.

Postoperative State. Between the third and fifth days after a major operation thermal coagulation points tended to increase and to maintain a higher level for one or two weeks; they gradually declined in the third or fourth weeks.

Gastrointestinal Disease (Non-neoplastic). In "nervous stomach," irritable colon, peptic

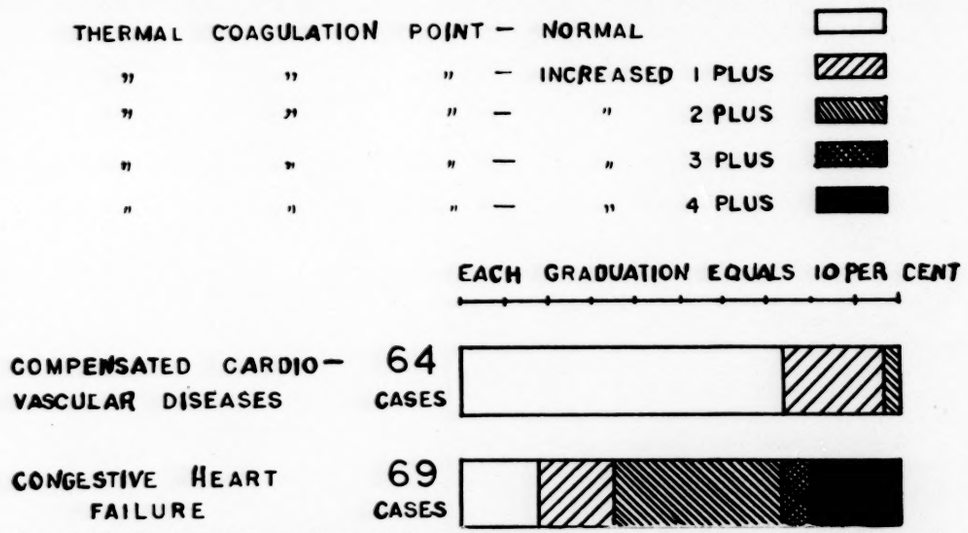

THERMAL COAGULATION POINT — NORMAL
" " " — INCREASED 1 PLUS
" " " — " 2 PLUS
" " " — " 3 PLUS
" " " — " 4 PLUS
EACH GRADUATION EQUALS 10 PER CENT
COMPENSATED CARDIO-VASCULAR DISEASES
64 CASES
CONGESTIVE HEART FAILURE
69 CASES

FIG. 1. Distribution of thermal coagulation point of blood serum in compensated cardiovascular diseases and congestive heart failure.

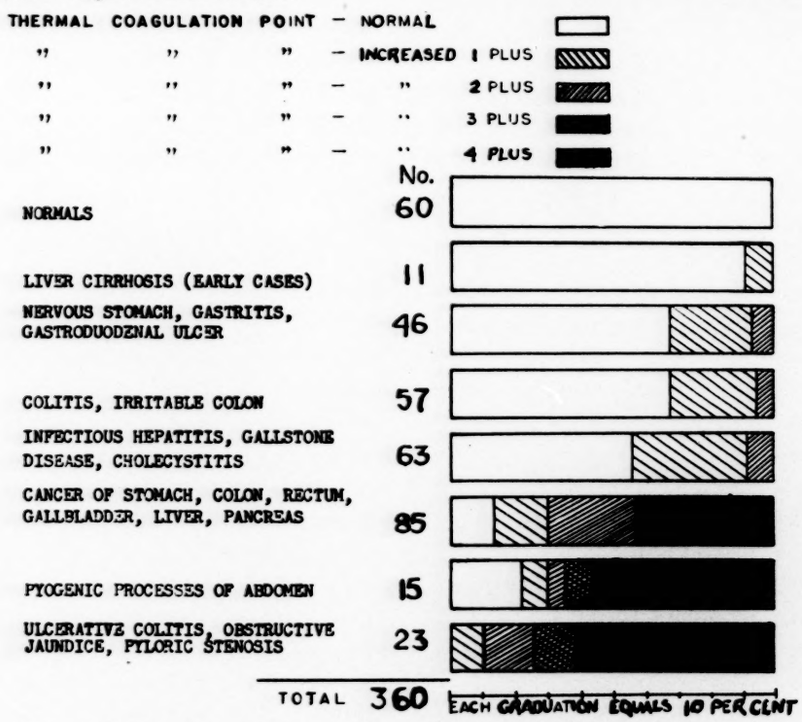

THERMAL COAGULATION POINT — NORMAL
" " " — INCREASED 1 PLUS
" " " — " 2 PLUS
" " " — " 3 PLUS
" " " — " 4 PLUS
No.
NORMALS 60
LIVER CIRRHOSIS (EARLY CASES) 11
NERVOUS STOMACH, GASTRITIS, GASTRODUODENAL ULCER 46
COLITIS, IRRITABLE COLON 57
INFECTIOUS HEPATITIS, GALLSTONE DISEASE, CHOLECYSTITIS 63
CANCER OF STOMACH, COLON, RECTUM, GALLBLADDER, LIVER, PANCREAS 85
PYOGENIC PROCESSES OF ABDOMEN 15
ULCERATIVE COLITIS, OBSTRUCTIVE JAUNDICE, PYLORIC STENOSIS 23
TOTAL 360
EACH GRADUATION EQUALS 10 PER CENT

FIG. 2. Distribution of thermal coagulation point of blood serum in sixty normal subjects and 300 patients with diseases of digestive organs.

ulcer, infectious or toxic hepatitis, hepatocellular jaundice and early cirrhosis thermal coagulation was usually normal. In pyogenic gastrointestinal disease (suppurative appendicitis, etc.), severe ulcerative colitis, protracted obstructive jaundice and pyloric stenosis the point was increased. (Fig. 2.)

disturbance suggests by inference the presence of a definite illness responsible for these changes.

The thermal coagulation of blood serum is subject to variations in the course of disease. Having determined the thermal coagulation point from two to seven times

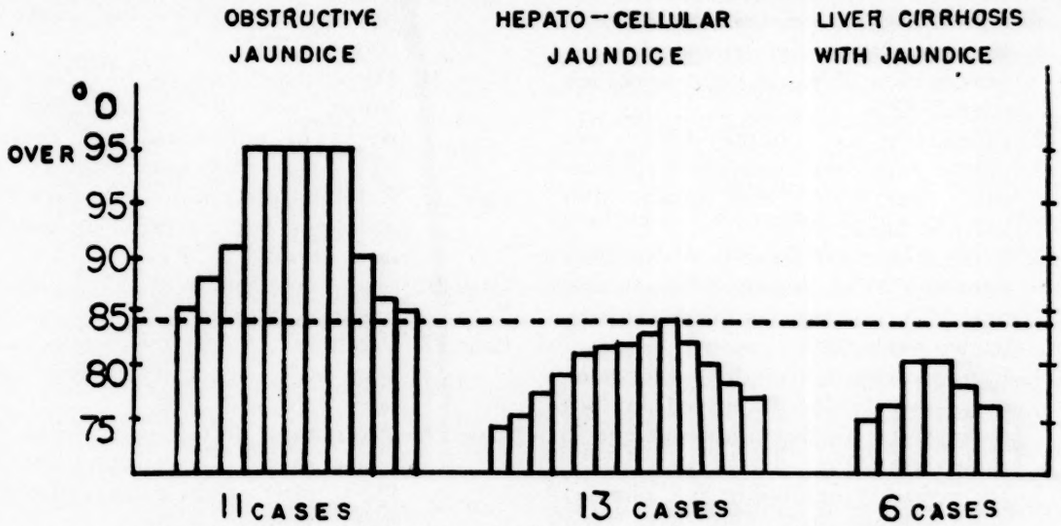


FIG. 3. Thermal coagulation point in thirty cases of jaundice of various origin.

Figure 3 is based on thirty cases of jaundice. Thermal coagulation was usually normal or borderline in hepatocellular jaundice or icterus due to early liver cirrhosis. Increases were frequent in obstructive jaundice particularly when this had existed for some time or was associated with malnutrition.

Miscellaneous Diseases. In most cases of pleurisy, glomerular nephritis, adnexitis, rheumatoid fever and infections of similar kind the thermal coagulation point was found to be normal or only rarely slightly increased. (Table II.)

In some severe anemias, in Graves' and Addison's disease thermal coagulation was found frequently increased. Table II includes some additional conditions in which thermal coagulation was moderately changed.

THERMAL COAGULATION POINT OF BLOOD SERUM AS A GENERAL INDICATOR OF ILLNESS

The test of thermal coagulation of blood serum offers a simple way to detect changes in serum proteins.[20] The existence of this

in about 200 cases at various intervals, we noted that it represents a kind of serologic correlate to the course of disease.

Brief reference will be made to fifty cases which represent only a small section of our observations, but which seem ample to substantiate this statement.

Case 1. Pneumonia, over 95°C.; after four weeks, recovery, 82°C.

Case 2. Pneumonia, over 95°C.; fall in temperature in two days, over 95°C.; recovery in ten days, 82°C.

Case 3. Pneumonia, over 95°C.; fall of temperature in four days, over 95°C.; recovery in ten days, 78°C.

Case 4. Pneumonia, over 95°C.; crisis on third day, 94°C.; improved two days later, 89°C.; recovery in seven days, 84°C.

Case 5. Atypical pneumonia, 92°C.; improved in four days, 84°C.; recovery in four days, 82°C.

Case 6. Atypical pneumonia, 88°C.; recovery in ten days, 81°C.

Case 7. Pneumonia, 90°C.; fall in temperature

in four days, 87°C.; recovery after seven days, 80°C.

Case 8. Cardiac failure, 88°C.; improvement in five weeks, 81°C.

Case 9. Cardiac failure, 86°C.; improved in ten days, 80°C.

Case 10. Nephrotic stage of glomerular nephritis, over 95°C.; in seven weeks edema gone, proteinuria less, 89°C.

Case 11. Nephrotic stage of glomerular nephritis, over 95°C.; in eight weeks less edema, 82°C.

Case 12. Pregnancy six months, 88°C.; one month later nephrosis and hypertension, over 95°C.; one month after induced labor, 84°C.

Case 13. Eclampsia, cesarean section; one week later over 95°C.; improved in five days, over 95°C.; almost complete recovery in two weeks, 80°C.

Case 14. Extensive burn, five days after accident, over 95°C.; improved in four days, 84°C.; further improvement in three days, 79°C.

Case 15. Incarcerated inguinal hernia, one day postoperative, 93°C.; six days later over 90°C.; ten days later improved, 89°C.; two weeks later recovery, 75°C.

Case 16. Extrauterine pregnancy, hematoma in pouch of Douglas, 83°C.; operation immediately, and one day later, 87°C.; three days later over 95°C.; one week later improved, 85°C.; and one week later recovered, 75°C.

Case 17. Pregnancy ninth month, 89°C.; three weeks later precipitate delivery at home and puerperal sepsis, over 95°C.; in four weeks improved, 86°C.

Case 18. Pregnancy, one day prepartum, 82°C.; ten days later mastitis, 86°C.; three days later suppuration, 88°C.; three weeks later improved, 86°C.; four weeks later recovered, 82°C.

Case 19. Inguinal herniorraphy (three days), 82°C.; ten days later infected wound, 86°C.; four weeks later recovery, 81°C.

Case 20. Acute appendicitis, fourth day, 83°C.; two days later 90°C.; seven days later, worse, over 95°C.; operation for appendiceal abscess and local peritonitis; two weeks later recovered, 82°C.

Case 21. Appendiceal abscess, over 95°C.; operation; two weeks later recovery, 82°C.

Case 22. Perforated appendix, diffuse peritonitis, over 95°C.; immediate operation; four days later over 95°C.; three weeks, improved, 88°C.; three weeks later further improvement, 84°C.

Case 23. Purulent pelvic inflammation, over 95°C.; one week, over 95°C.; operation; two weeks later considerable improvement, 85°C.; two weeks later recovery, 81°C.

Case 24. Purulent perimetritis, 87°C.; one week worse, over 95°C.; operation; two weeks of antibiotics and drainage, 82°C.; two weeks later recovery, 78°C.

Case 25. Retained placenta, sepsis, over 95°C.; one week later, over 95°C.; one week later improved, 79°C.

Case 26. Septic abortion, over 95°C.; curettage; five days improved, 84°C.

Case 27. Pyothorax, 80°C.; five weeks, worse, over 95°C.; operation; three weeks later improved, 76°C.

Case 28. Pyothorax, 86°C.; two weeks later worse, over 95°C.; ten days later over 95°C.; three weeks conservative treatment, improved, 82°C.

Case 29. Pyothorax, over 95°C.; four weeks conservative treatment, improved 86°C.

Case 30. Phlegmon of extremities, over 95°C.; incision, antibiotics; two weeks improved, 92°C.; two weeks later recovery, 78°C.

Case 31. Phlegmon of extremities, over 95°C.; incision, antibiotics; two weeks recovery, 83°C.

Case 32. Multiple sclerosis, decubitus ulcers, 74°C.; secondary infection, phlegmon, two weeks later, 89°C.; two weeks later worse, over 95°C.; death two days later.

Case 33. Carcinoma of esophagus, 79°C.; three weeks later worse, over 95°C.; death three weeks later.

Case 34. Inoperable carcinoma of stomach, 83°C.; three weeks later worse, 86°C.; three months later, 92°C.; death six weeks later.

Case 35. Inoperable carcinoma of colon with ascites, 86°C.; ten days later worse, over 95°C.; death one week later.

Case 36. Carcinoma of pancreas, 89°C.; one month later worse, over 95°C.; death two weeks later.

Case 37. Metastatic carcinoma of liver, 85°C.;

worse one month later, over 95°C.; death two weeks later.

Case 38. Metastatic carcinoma of liver, 86°C.; three weeks later worse, 87°C.; exploratory laparotomy; one month later over 95°C.; two months later over 95°C.; death three weeks later.

Case 39. Carcinoma of colon with hepatic metastasis, 87°C.; two weeks later worse, over 95°C.; one week later death.

Case 40. Gallstones with obstructive jaundice, over 95°C.; two months later improved, 77°C.; no operation; one year later readmitted for carcinoma of gallbladder, 87°C.; exploratory laparotomy; one month later over 95°C.; death in ten weeks.

Case 41. Active pulmonary tuberculosis, 77°C.; two months later worse, over 95°C.; death in one week.

Case 42. Active pulmonary tuberculosis, 80°C.; three weeks later worse, 90°C.; two weeks later still worse, over 95°C.; one month later death.

Case 43. Active pulmonary tuberculosis, 83°C.; two weeks later much worse, 95°C.; death ten weeks later.

Case 44. Active pulmonary tuberculosis, 80°C.; two months later worse, 84°C.; two months later still worse, 90°C.; death in one month.

Case 45. Cardiac failure, 85°C.; two months later worse despite treatment, 93°C.; death one week later.

Case 46. Cardiac failure, 85°C.; four days later much worse, 93°C.; death one week later.

Case 47. Cardiac failure, 83°C.; six months later worse despite treatment, 88°C.; death three months later.

Case 48. Cardiac failure, 84°C.; six weeks later worse despite treatment, over 95°C.; death in two weeks.

Case 49. Cardiac failure, 84°C.; three weeks later worse, 90°C.; one month later over 95°C.; death in two weeks.

Case 50. Cardiac failure, 87°C.; two months later worse, over 95°C.; death in two more weeks.

These data indicate that the thermal coagulation point may undergo changes in the same individual rather rapidly. It follows to a great extent the course of the disease, increasing with advance, decreasing with improvement and reverting to normal with recovery.

Table 3 presents the follow-up studies of 179 cases of cancer, pulmonary tuberculosis and severe cardiac disease with failure. All were treated and followed for periods up to one year after the determination of thermal coagulation. The survival time during this year was determined.

In chronic and fatal diseases the level of thermal coagulation seemed to give some indication concerning the survival time. In general the greater the defect in thermal coagulation the shorter was the survival time in these groups of diseases. A 4 plus increase appeared to mean a short survival time in cancer, pulmonary tuberculosis (streptomycin was not available) and cardiac failure. Particularly in cancer if the change of thermal coagulation was very pronounced, the growth had extended widely (infiltration or metastasis), broken down, or profoundly reduced general nutrition (hypoproteinemia, hypalbuminemia). In these cases the tumor was usually inoperable and the survival time after operation was short. Among thirty-two patients with cancer of abdominal viscera and a 4 plus increase in thermal coagulation one-half died within one month from the date of performing the test and all died within three months.

COMMENT

The thermal coagulation point of blood serum is an easy non-specific serologic test of illness, irrespective of its neoplastic or non-neoplastic character. This is its main application in disease. Changes in thermal coagulation imply the existence of an underlying pathologic process responsible for this serologic disorder. It follows the course of disease and swings in both directions according to the trend of illness.

The clinical significance of changes in thermal coagulation point of blood serum differs in various pathologic disorders. The first thirty aforementioned cases demon-

strate that in acute disorders the increase in thermal coagulation is transient; it vanishes with improvement of the patient and provides information concerning only the stage of disease but none with respect to the gravity or prognosis of the underlying pathologic disorder. This situation prevails in pneumonia, pregnancy, pyogenic infections, malaria, malnutrition, postoperative conditions, burns, etc. Increased thermal coagulation reverts to normal with clinical improvement.

On the other hand, in serious and often fatal diseases like cancer, tuberculosis, Hodgkin's disease and cardiac failure defective thermal coagulation often reflects the gravity of the situation, the extent and irreversibility of the underlying process. In Cases 33 to 50 this statement finds support.

If our findings are confirmed on a broader scale, they may have definite prognostic value for evaluating the survival time of patients with fatal diseases, especially in cancer patients. They may also afford some clue to the operability of the tumors.

SUMMARY AND CONCLUSIONS

The thermal coagulation point of 1,500 sera was determined by the method described in sixty normal subjects and 1,100 patients including 162 cases of cancer. This point is the minimal temperature, acting for one minute, sufficient to coagulate the serum *en bloc* so that it loses its thixotropy and does not break under standardized succussion. Values of 75° to 80°C. are normal, 81° to 83°, 84° to 89°, 90° to 95° and over 95°C. are considered increased 1, 2, 3 and 4 plus, respectively.

The thermal coagulation point has been observed to be increased in many patients with malignant tumors, particularly of the abdominal organs, in 100 per cent of pregnancy with complications, in lipoid and lower nephron nephrosis, extensive burns and frostbite. Increases were almost invariable in ulcerative colitis, pyloric stenosis and prolonged obstructive jaundice. The same situation existed in pyogenic processes of the abdomen, chest and extremities. Acute massive infections as well as advanced lymphogranulomatosis and leukemia also produced positive tests. About two-thirds of patients with heart failure and more than 40 per cent of pregnant women (usually late in pregnancy) as well as a fairly large percentage of individuals with advanced pulmonary tuberculosis showed an increased thermal coagulation point.

The thermal coagulation point of blood serum is a readily performed, non-specific serologic indicator of illness. It follows to a great extent the course of the disease, increasing with deterioration, decreasing with improvement and reverting to normal with recovery. In many acute illnesses it swings in both directions and seems to lack prognostic value, but in some chronic diseases its level reflects the gravity of the lesion, invasiveness and concomitant nutritional disturbances. In these diseases it may aid in determining the probable survival time. Among sixty cases of cancer, pulmonary tuberculosis and heart failure showing an increase above 95°C., all but three died within three months.

Changes in the thermal coagulation point imply the existence of an underlying pathologic process responsible for the serologic abnormality. The incidence of defective thermal coagulation of the serum in disease differs from that of most other non-specific serological tests.

The Thermal Coagulation Point of Blood Serum*

II. Significance of the Principle of Defective Thermal Coagulation for Diagnosis of Cancer

GEORGE B. JERZY GLASS, M.D.
New York, New York

THIS paper deals with studies on thermal coagulation point of blood serum which concern the problem of cancer. The data may assist in the interpretation of the significance of the defective thermal coagulation for the diagnosis of cancer. A test based upon a similar principle has recently been suggested by Huggins et al.[1,2] for detection of malignancy. Its clinical evaluation and relationship to thermal coagulation point of serum are reported elsewhere.[4,7]

MATERIAL AND METHOD

The thermal coagulation point of blood serum was determined in 162 cases of malignancy by the method described in Part I. The diagnosis was verified in every case by biopsy, operation or postmortem examination.

RESULTS

In Table I are listed in abbreviated form the data obtained in 162 cases of cancer and in sixty normal subjects, forty-four cases of non-complicated pregnancy and 894 cases of various non-neoplastic diseases. For simplification the cases with defective thermal coagulation of blood serum (2–4 plus) were grouped together.

Table I shows that in malignancies the greatest deviations of thermal coagulation point were found in neoplasms of abdominal

TABLE I
DEFECTIVE THERMAL COAGULATION OF BLOOD SERUM IN VARIOUS NEOPLASTIC AND NON-NEOPLASTIC DISEASES

Diagnoses	No. of Cases	Increased (above 83°C.) Thermal Coagulation Point	
		No. of Cases	Percentage
I. Normal Subjects (Total)	60	0	0
II. Malignant Tumors of (Total)	162	85	52.5
Abdominal viscera	85	60	70.6
Bones, thyroid, prostate	19	12	63.1
Breast	11	3	27.3
Skin, lip, tongue	14	3	21.4
Lung	8	2	25.0
Cervix, uterus	25	5	20.0
III. Normal, Mainly Late, Pregnancy (Total)	44	19	43.2
IV. Non-neoplastic Diseases (Total)	894	292	32.6
(a) Frequently associated with disturbed thermal coagulation: complicated pregnancy, nephrosis, eclampsia, extensive burns, frostbite, ulcerative colitis, pyloric stenosis, obstructive jaundice, bacterial endocarditis, typhoid, pyogenic infections of abdominal and chest organs and extremities, acute malaria, congestive heart failure, Hodgkin's disease, pneumonia, pulmonary tuberculosis, acute and subacute arthritis (Total)	407	247	60.7
(b) Infrequently associated with disturbed thermal coagulation: inflammatory (non-pyogenic) diseases: pleurisy, adnexitis, glomerulonephritis, lymphadenitis, bronchitis, gastritis, cholecystitis, infectious hepatitis, colitis, uncomplicated diabetes mellitus, peptic ulcer without malnutrition, anemias of various type, emphysema, bronchial asthma and other allergic conditions, uterine fibroids, fractures, functional disturbances of the stomach and colon, other miscellaneous conditions (Total)	487	45	9.3
Total	1160	396	34.1

* From the Department of Medicine, The New York Medical College, Flower and Fifth Avenue Hospitals, New York, N. Y.

viscera (70.6 per cent) and in tumors of the bones, thyroid and prostate (63.3 per cent). The incidence of change in cancer of other organs was much smaller and a defective thermal coagulation point was found only in thirteen of fifty-eight cases of cancer of the female genital organs, breasts, skin, lip, tongue and lungs, i.e., in 22.4 per cent.

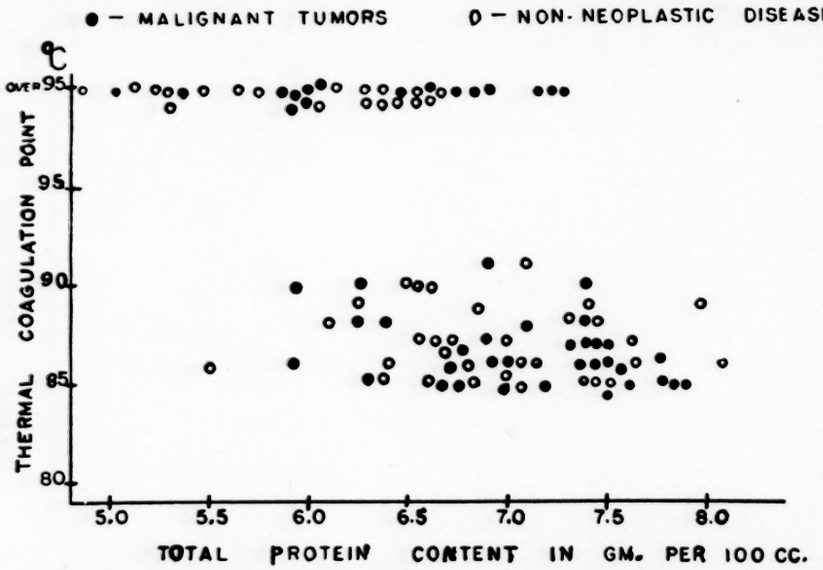


FIG. 1. Correlation of thermal coagulation point and total serum proteins in 100 cases of malignant tumors and non-neoplastic disease associated with defective thermal coagulation of serum.

The data listed in Table 1 and discussed in Part I of this paper indicate that increased thermal coagulation point of blood serum is not specific for cancer, having been found in many non-neoplastic diseases. The percentage of "false positive tests" (i.e., defective thermal coagulation in non-neoplastic diseases) amounted to 32.6 per cent of the total studied (292 cases with defective thermal coagulation among 894 cases). If the cases are selected among diseases which are known to be associated frequently with disturbances in serum proteins (nephrosis, eclampsia, complicated pregnancy, extensive burns and frostbite, ulcerative colitis, pyloric stenosis, obstructive jaundice, bacterial endocarditis, pyogenic infections, malaria, pneumonia, pulmonary tuberculosis, acute and subacute arthritis, congestive heart failure, Hodgkin's disease), the percentage of false positive tests would be much greater and would amount to 60.7 per cent (247 of 407 cases studied).

If the control cases are selected among other non-neoplastic conditions so that the aforementioned disorders are excluded, the percentage of "false positive tests" will be very small and would amount only to 9.3 per cent in this material. In this group of cases, increased thermal coagulation point was found in only forty-five of the total of 487 cases studied (listed under IV*b* in Table I).

Figure 1 shows the correlation scatter diagram of total serum protein content and thermal coagulation point in 100 cases of neoplastic and non-neoplastic diseases presenting an abnormally increased thermal coagulation point. The protein contents of the serum were determined by methods described in Part III. It is readily apparent from Figure 1 that cancer sera do not differ from pathologic non-neoplastic sera in regard to the correlation of these two features.

Figure 2 deals with chronic diseases of the digestive tract. It shows that a normal thermal coagulation point of blood serum is found about three times more frequently in non-neoplastic than in neoplastic diseases of the digestive tract. On the other hand a 2 or 3 plus increase in thermal coagulation was found more than three times, and a 4 plus increase more than seven times as

frequently in cancer of digestive tract than in non-neoplastic diseases of the same organs.

In Figure 3 are listed data obtained in forty-four cases of ascites of various origin. It is evident from this figure that ascites due to intra-abdominal malignancy was associated with a definite increase of the thermal coagulation point. The same increase was noted in ascites due to nephrosis, heart failure and a few cases of advanced hepatic cirrhosis with peripheral edema and hypoproteinemia (which are not listed in the figure). In early cirrhosis without edema a normal thermal coagulation point was consistently observed.

COMMENT

The evidence submitted in this paper indicates that the thermal coagulation point of blood serum has only limited application in cancer detection. The high incidence of "false negative tests" (normal coagulation in cancer) precludes the use of the principle of defective thermal coagulation as an indicator of early cancer. Most false negative results were observed in early cancers of the genitalia, breast, lung and skin. The average percentage of false negative tests in all our cancer cases was high (47.4 per cent).

This percentage of false negative tests in cancer can be decreased to 32.1 per cent by including small deviations in thermal coagulation (1 plus increase) and considering them pathologic. On the other hand this would greatly increase the percentage of false positive tests in cancer and reduce its diagnostic significance even more.

The incidence of "false positive tests" (abnormal thermal coagulation in non-neoplastic diseases) was very high in our material, and again indicated that the principle of defective thermal coagulation could not be used for cancer diagnosis. This high incidence occurred because the non-neoplastic control cases were selected mainly among patients with severe illness, on the wards of a general hospital and not at random in the outpatient department. This type of control is needed to provide a true

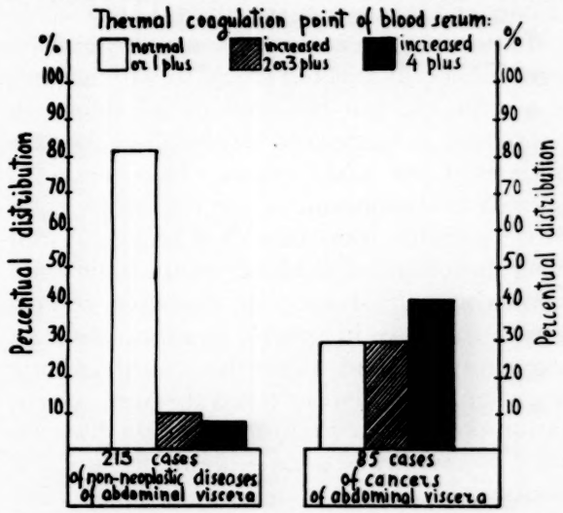

Thermal coagulation point of blood serum:
normal or 1 plus
increased 2 or 3 plus
increased 4 plus
%
Percentual distribution
215 cases of non-neoplastic diseases of abdominal viscera
85 cases of cancers of abdominal viscera

FIG. 2. Percentile distribution of thermal coagulation point in 300 cases of various diseases of abdominal viscera.

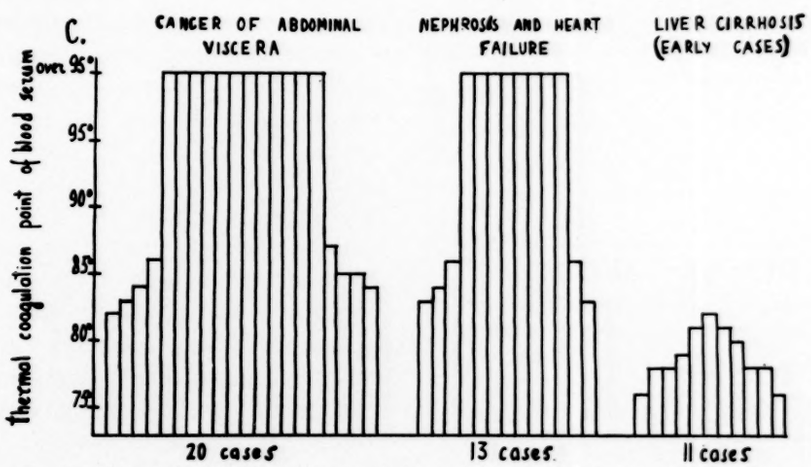


FIG. 3. Thermal coagulation point of blood serum in forty-four cases of ascites of various origin.

background of the specificity of this test for cancer.

To calculate the thermal coagulation defect in terms of the total protein content does not alter the diagnostic significance of defective thermal coagulation for diagnosis of cancer and its non-specificity.

The test may have some diagnostic significance in selected cases, in which there is a wide margin between its incidence in neoplastic as compared with non-neoplastic disease of the same organ. This seems to prevail in carcinoma of the digestive tract. Since a highly increased (3–4 plus) thermal coagulation point of blood serum in chronic non-neoplastic disease of digestive organs was found only in pyloric stenosis, obstructive jaundice and ulcerative colitis of long duration, a highly increased thermal coagulation point, after exclusion of these diseases, may be indicative of possible malignancy of abdominal viscera in patients with digestive disturbances.

Determination of the thermal coagulation point is helpful in the differential diagnosis of ascites. A low thermal coagulation point in a patient with ascites tends to exclude a neoplastic origin and suggests cirrhosis, while a high thermal coagulation point strongly indicates malignancy if cardiac and renal factors can be excluded and no other edema or transudation is found.

SUMMARY AND CONCLUSIONS

The thermal coagulation point of blood serum was determined in 162 cases of cancer and compared with data obtained in sixty normal subjects, forty-four pregnant women and 894 cases of non-neoplastic disease. Defective thermal coagulation, as evidenced by increased thermal coagulation point of blood serum, was found in 70.6 per cent of carcinomas of the gastrointestinal tract and of the bile passages and liver, in 63.1 per cent of malignant tumors of bones, thyroid and prostate, but only in 22.4 per cent of cancer of the female genitalia, breast, skin, lip, tongue and lungs.

The defective thermal coagulation of blood serum is an easily performed, non-specific, serologic index of general illness. Owing to its non-specificity, as evidenced by the large percentage of "false positive" (32.6 per cent) and "false negative" tests (47.4 per cent), this principle cannot be used to screen early cancer in the population at large.

The Thermal Coagulation Point of Blood Serum*

III. Correlation with Serum Proteins, Sedimentation Rate and Weltmann Reaction

GEORGE B. JERZY GLASS, M.D.
New York, New York

THE purpose of this paper is to determine the relationship of the disturbance in thermal coagulation of blood serum to total protein, albumin and globulin content of the serum and its correlation with other non-specific serologic protein tests, namely, sedimentation rate and Weltmann heat flocculation reaction.

MATERIAL AND METHODS

The thermal coagulation point of blood serum in forty-three cases was compared with the total albumin and globulin content of the serum, utilizing an improved Howe's method,[21,22] with the sedimentation rate in sixty cases using the Westergren technic, and with the Weltmann heat flocculation reaction, as determined by the original Weltmann method[6] in 200 sera. In addition we reviewed the data on 400 total serum proteins[20] (determined by the Kjeldahl method and partly by refractometer) and compared them with the thermal coagulation point of the same sera, determined by the technic described in Part I of this paper.

The subjects examined included normal controls and patients with non-neoplastic diseases and diverse malignancies. In the cases of malignancy, biopsy, excised tissue or postmortem examination confirmed the diagnosis.

RESULTS

Thermal Coagulation of Blood Serum and Total Serum Proteins. The data on 400 simultaneous determinations of thermal coagulation point and total serum proteins are reproduced in the form of a scatter diagram in Figure 1. Additional data concerning forty-three other cases are listed in Table I.

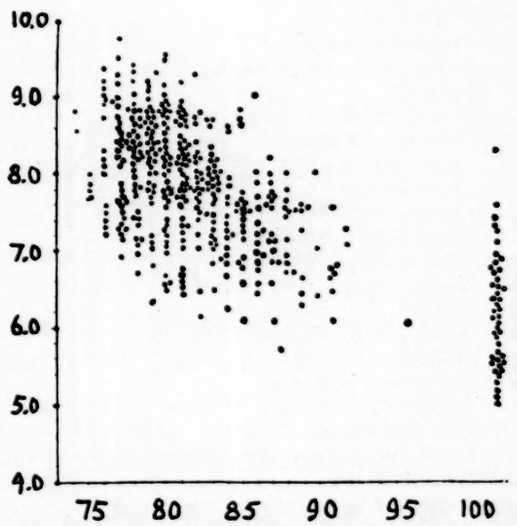


FIG. 1. Thermal coagulation point (°C.) and total protein content of serum (gm. per cent) in 400 individuals.

Figure 1 shows that with a normal protein content (6.5–7.9 gm. per cent),[29] the thermal coagulation point of the serum may be low, normal and moderately or greatly increased. On the other hand, in the twenty-one cases of Figure 1 and in ten cases of Table I, with

* From the Department of Medicine, The New York Medical College, Flower and Fifth Avenue Hospitals, New York, N. Y.

a total protein content below 6.0 gm. per cent, the thermal coagulation point was decidedly increased.

There is no absolute correlation between total protein content and thermal coagulation. However, a general trend is evident toward higher thermal coagulation points with lowering of the total protein values in the serum.

Thermal Coagulation of Blood Serum and Its Total Globulin Content. In Table 1 are listed simultaneous determinations of total albumin and globulin content and thermal coagulation point of blood serum in forty-

TABLE 1

TOTAL PROTEINS, ALBUMINS, GLOBULINS AND THERMAL COAGULATION POINT OF THE BLOOD SERUM IN FORTY-THREE PATIENTS WITH VARIOUS PATHOLOGIC LESIONS

Case No.	Diagnoses	Serum Albumins gm./100 cc.	Serum Globulins gm./100 cc.	Total Serum Proteins gm./100 cc.	Thermal Coagulation Point (°c.)
1	Carcinoma of uterus	5.2	3.0	8.2	normal (79)
2	Carcinoma of prostate	5.3	2.5	7.8	2 plus (86)
3	Pneumonia	4.4	3.2	7.6	2 plus (87)
4	Peripheral phlegmon	4.6	3.0	7.6	2 plus (86)
5	Nervous indigestion	4.7	3.0	7.7	normal (79)
6	Active pulmonary tuberculosis	4.8	2.7	7.5	2 plus (88)
7	Carcinoma of colon	5.1	2.4	7.5	2 plus (86)
8	Duodenal ulcer	5.1	2.4	7.5	1 plus (83)
9	Heart failure	4.3	3.1	7.4	2 plus (86)
10	Peripheral gangrene	5.1	2.3	7.4	2 plus (88)
11	Acute rheumatic polyarthritis	4.6	2.8	7.4	1 plus (82)
12	Normal	4.8	2.6	7.4	normal (80)
13	Carcinoma of rectum	4.9	2.5	7.4	2 plus (86)
14	Carcinosis of peritoneum	4.4	3.0	7.4	3 plus (90)
15	Carcinoma of colon	5.5	1.9	7.4	normal (80)
16	Cholelithiasis	4.5	2.7	7.2	normal (78)
17	Ovarian carcinoma	4.7	2.5	7.2	4 plus (>95)
18	Pancreatic carcinoma	5.0	2.2	7.2	4 plus (>95)
19	Carcinosis of peritoneum	4.9	2.3	7.2	4 plus (>95)
20	Sarcoma of scapula	4.7	2.4	7.1	2 plus (88)
21	Normal	4.6	2.5	7.1	normal (75)
22	Metastatic carcinoma of liver	3.8	3.2	7.0	2 plus (86)
23	Normal	4.6	2.4	7.0	normal (77)
24	Carcinoma of stomach	5.1	1.9	7.0	2 plus (87)
25	Carcinoma of cervix	4.3	2.6	6.9	3 plus (91)
26	Late pregnancy	4.1	2.8	6.9	2 plus (87)
27	Active pulmonary tuberculosis	4.1	2.2	6.3	4 plus (>95)
28	Late pregnancy	4.7	1.6	6.3	1 plus (83)
29	Heart failure	4.0	2.3	6.3	4 plus (>95)
30	Carcinoma of liver	3.6	2.7	6.3	3 plus (90)
31	Hodgkin's disease	3.6	2.5	6.1	4 plus (>95)
32	Complicated pregnancy	4.4	1.7	6.1	2 plus (88)
33	Addison's disease	3.5	2.4	5.9	4 plus (>95)
34	Bronchogenic carcinoma	4.4	1.5	5.9	1 plus (82)
35	Carcinoma of breast	4.2	1.7	5.9	3 plus (90)
36	Carcinoma of stomach	3.1	2.8	5.9	4 plus (>95)
37	Carcinoma of stomach	3.2	2.2	5.4	4 plus (>95)
38	Lymphatic leukemia	3.5	1.8	5.3	4 plus (>95)
39	Ulcerative colitis with malnutrition	3.8	1.4	5.2	4 plus (>95)
40	Lipoid nephrosis	3.2	1.9	5.1	4 plus (>95)
41	Carcinoma of stomach	3.1	1.9	5.0	4 plus (>95)
42	Nephrosis	2.9	2.0	4.9	4 plus (>95)
43	Nephrotic stage of nephritis	1.8	2.9	4.7	4 plus (>95)

three cases of neoplastic and non-neoplastic diseases. The material was selected mainly from cases showing increased thermal coagulation so that only eleven of these cases had a normal or borderline value of thermal coagulation. These cases are grouped according to decreasing total protein content.

4.0 gm. per cent (Cases 22, 30, 31, 33, 36 to 43) the thermal coagulation point in ten of eleven cases showed a 4 plus increase and this occurred in neoplastic as well as in non-neoplastic diseases.

With a normal albumin content (4.7–5.7 gm. per cent)[23] the thermal coagulation

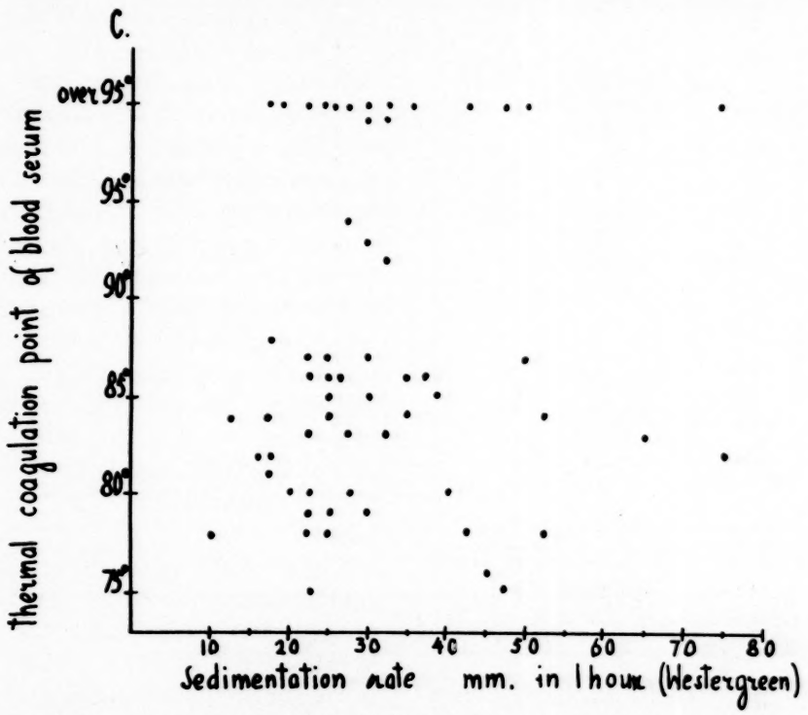


FIG. 2. Thermal coagulation point of blood serum and sedimentation rate in sixty patients.

It is evident from the data of Table 1 that the thermal coagulation point may be high or low at any total globulin value and vice versa. If the total globulin levels and thermal coagulation points are grouped in the form of a correlation scatter diagram, no correlation between them is found and the points are scattered throughout the figure.

There is no correlation between total globulin content of the serum and its thermal coagulation point.

Thermal Coagulation of Blood Serum and Its Albumin Content. The data are listed in Table 1. Of twenty-two cases in this table showing a serum albumin content below 4.5 per cent, an increased thermal coagulation point (2, 3 or 4 plus) was found in twenty-one. With an albumin level below

point was either normal or increased. Among fourteen of these cases the thermal coagulation was moderately or greatly increased in nine in spite of normal albumin and globulin levels (Cases 2, 6, 7, 10, 13, 17, 18, 19, 24).

In hypalbuminemia the thermal coagulation point was always found to be increased. However, hypalbuminemia does not seem to be the sole reason for defective thermal coagulation of blood serum, since the latter was found also in absence of hypalbuminemia.

Thermal Coagulation of Blood Serum and Sedimentation Rate. In Figure 2 are shown results of simultaneous determinations of thermal coagulation point and sedimentation rate. These data indicate that the

sedimentation rate at the same level of thermal coagulation point may be low, normal or high, and the thermal coagulation point may be normal, moderately or greatly increased with the same sedimentation rate. Only in a small percentage of these cases is there a concordance between high sedimentation rate and high levels of thermal coagulation point. In most of the cases no correlation whatever is found.

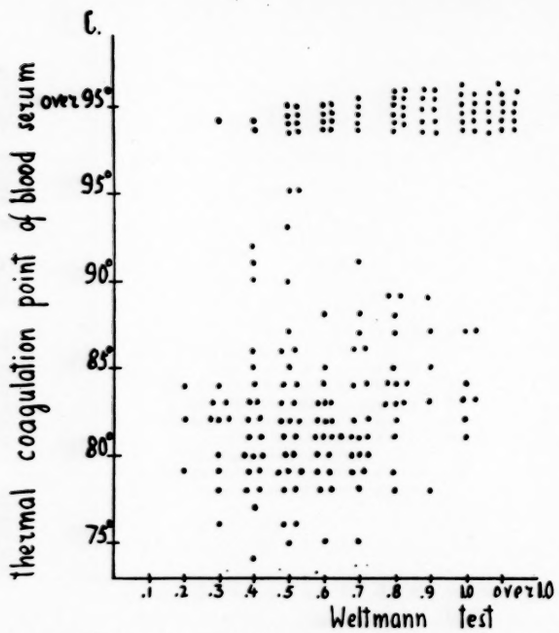


FIG. 3. Thermal coagulation point of blood serum and Weltmann test in 200 patients.

From these data it would appear that there is no correlation between the thermal coagulation level and the sedimentation rate. This may be explained by the fact that the thermal coagulation point is determined in serum while the sedimentation rate depends largely upon disturbances in plasma fibrinogen, as shown by Westergren et al.,[24] Gray and Mitchell,[25] Oakley[26] and others. If parallel deviations of both tests occur in some instances, this would depend upon the presence of other disturbances in blood which also influence the sedimentation rate (altered red blood cell count, presence of products of cellular disintegration, variations in some globulin fractions) and which may cause or be associated with deviations in thermal coagulation of blood serum. For the same reason the heat coagulation test of Black, Kleiner and Bolker,[3] which is performed on plasma and depends mainly upon disturbances in the fibrinogen content of the blood, is based on observations different from those noted in respect to thermal coagulation of blood serum.

Thermal Coagulation of Blood Serum and Weltmann Heat Flocculation Reaction. The data obtained in 200 sera are summarized in Figures 3, 4 and 5. The numbers (0.1–1.0) denominating the Weltmann test correspond to concentrations of calcium chloride per thousand used in the reaction. Each point shows the minimal calcium chloride concentration sufficient to cause definite flocculation ("g" reaction of Weltmann). Positive reactions at concentrations of 0.4–0.5 are considered normal values; those of 0.6 or higher as "shift to the left" or "narrowing of the band"; and those of 0.3 or lower as "shift to the right" or "widening of the band."

Figure 3 shows that there is absolutely no correlation between the level of the thermal coagulation point and the result of the Weltmann test. The points are scattered throughout the diagram and high and low levels of thermal coagulation point are found at any values of the Weltmann test and vice versa. Only in a rather small number of pathologic cases is there a simultaneous increase in thermal coagulation point and a shift of the Weltmann test to the left.

In Figures 4 and 5 the shifts in Weltmann test and in thermal coagulation point of blood serum occurring in the course of disease are based upon eighty-seven simultaneous determinations of both tests in thirty cases of non-neoplastic diseases. One-half of these cases show complete discordance between the direction of the shifts in both tests in the course of disease; the data listed in Figure 4 confirm the lack of correlation between these tests. In Figure 5 cases are grouped which show a similar trend of shifts in the Weltmann test and

thermal coagulation point during the course of disease.

Although the general trend of change in these cases is concordant in respect to both tests, it is evident (also in Figure 5) that the absolute levels of both tests in several instances are in complete disagreement with each other; at one time one test, at another the other shows more extensive deviation. Most concordant deviations in both tests seem to occur in pyogenic processes and in severe infectious diseases. In other conditions there is some dissociation between the tests. In nephrosis, cardiac failure and cancer the results of thermal coagulation are more prominent while in localized inflammatory processes those of the Weltmann test are more obvious.

Since only in about half of pathologic sera a correlation could be found between thermal coagulation and Weltmann reaction, the mechanisms involved in both tests

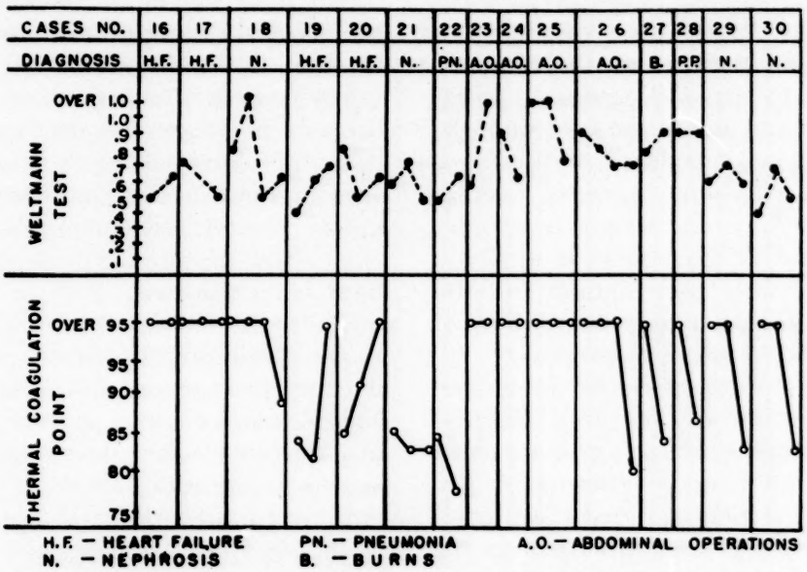

CASES NO. 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
DIAGNOSIS H.F. H.F. N. H.F. H.F. N. PN. A.O. A.O. A.O. A.O. B. P.P. N. N.
WELTMANN TEST
OVER 1.0
THERMAL COAGULATION POINT
OVER 95
95
90
85
80
75
H.F. — HEART FAILURE
N. — NEPHROSIS
PN. — PNEUMONIA
B. — BURNS
A.O. — ABDOMINAL OPERATIONS

FIG. 4. Discordant deviations in Weltmann test and thermal coagulation point in fifteen patients.

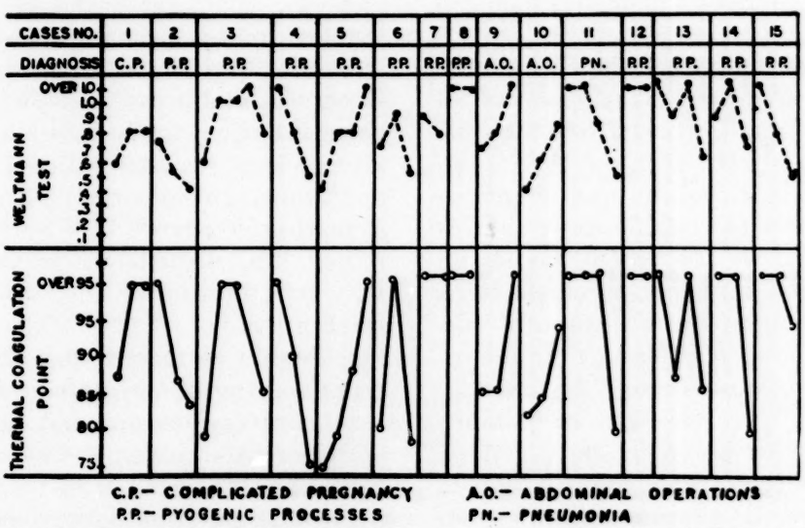

CASES NO. 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
DIAGNOSIS C.P. P.P. P.P. P.P. P.P. P.P. P.P. P.P. A.O. A.O. PN. P.P. P.P. P.P. P.P.
WELTMANN TEST
OVER 10
THERMAL COAGULATION POINT
OVER 95
95
90
85
80
75
C.P. — COMPLICATED PREGNANCY
P.P. — PYOGENIC PROCESSES
A.O. — ABDOMINAL OPERATIONS
PN. — PNEUMONIA

FIG. 5. Concordant deviations in Weltmann test and thermal coagulation point in fifteen patients.

are different. The Weltmann test seems to depend, like other flocculation tests, at least partly upon disturbances in euglobulins, whereas the thermal coagulation shows no relation to this factor.

COMMENT

The data just presented on the relationship between the thermal coagulation point, serum proteins and some non-specific serologic tests must be considered preliminary. They require extension by new protein fractionation technics and should be supplemented by some modern protein serologic tests. More precise information on the mechanism of the thermal coagulation of blood serum may then be obtained.

The role of gamma-globulins (euglobulins) in production of defective thermal coagulation is apparently subordinate since the heat gelification or coagulation *en bloc* of serum is not dependent upon this fraction.[39] The serum gamma-globulins in the presence of electrolytes and under the influence of heat have been observed to show a characteristic heat flocculation only.[5,6]

The lack of correlation between increase in euglobulins and thermal coagulation of blood serum is also supported by the lack of close relationship between the Weltmann reaction, dependent mainly upon euglobulins and the thermal coagulation point. It is also evidenced by the recent studies on gamma-globulins and on serologic tests based mainly upon gamma-globulin disturbances, such as the Hanger cephalin-cholesterol flocculation test and the colloidal gold reaction.[5,27,28] The sera of patients with hepatocellular jaundice, early hepatic cirrhosis and acute glomerulonephritis which have an increased gamma-globulin content[29–32] and a highly positive cephalin-cholesterol or colloidal gold test[28,33] almost constantly have a normal thermal coagulation point of blood serum.[20] The sera of patients with nephrosis, malignancy of the gastrointestinal tract or severe malnutrition most frequently show highly increased thermal coagulation point of blood serum (see Part I and II), but they usually have a normal or low gamma-globulin content[32,34,35] and a negative cephalin-cholesterol flocculation test if no major impairment of the liver co-exists.

We have as yet no data on the role of alpha- and beta-globulins in affecting the level of thermal coagulation. This is certainly worth further study because in diseases in which the thermal coagulation point of blood serum is usually increased (carcinoma of abdominal viscera, nephrosis, severe tuberculosis, pneumonia, rheumatic fever) high alpha- and beta-globulin values have been reported.[9,36–38]

There is considerable evidence pointing to the predominant role of serum albumins in the production of defective thermal coagulation of blood serum: (1) The role of albumins in the process of heat gelification is firmly established.[4,39] (2) The thermal coagulation point is always increased, as shown above, in cases of marked hypalbuminemia. (3) We found (see Part I and II) an increased thermal coagulation point of blood serum most frequently in diseases known to be associated with hypoproteinemia and hypalbuminemia, such as nephrosis, malnutrition, malignancies of the gastrointestinal tract, pyloric stenosis, ulcerative colitis, extensive burns, after major operations, in malaria, Addison's disease, hyperthyroidism.[9,35,40–42] and also in pregnancy. The disturbance in serum albumin may be quantitative (hypalbuminemia) or qualitative.

A highly increased thermal coagulation point was found, however, in several pathologic sera (neoplastic and non-neoplastic) with normal content of total albumins and globulins. (Table I.) If further studies show a normal globulin pattern in these cases, this finding would suggest the possibility of a qualitative change in the albumin fraction evidenced only by modification of the thermal coagulation point.

The role of qualitative changes in serum albumins as the main factor producing defective thermal coagulation of blood serum in cancer has also been evoked

recently by Huggins et al.[1,2] independently of our earlier suggestion.[20] They based this assumption on their studies of the defective thermal coagulation of serum in pathologic conditions as determined by the iodoacetate index of serum.

Perhaps disturbances in albumins are not the only cause of defective thermal coagulation of blood serum. It can safely be stated that each of the non-specific serologic protein tests depends upon one main factor and several additional subordinate factors. This is exemplified by the great dependence of the Hanger test upon the gamma-globulins, but also from the imbalance between the flocculating effect of the latter and the inhibiting effect of albumins[33,43] and lipoproteins.[5] It is evidenced also by the important role of lipids[44] in the Maclagan thymol turbidity test[45] but its additional dependence upon interaction of gamma-globulins.[5,46] In the same way the thermal coagulation point of blood serum seems to depend largely upon disturbances in the serum albumins (hypalbuminemia and perhaps "dysalbuminemia"). But as with the other serologic tests it may also depend upon changes in some other components of the serum, such as alpha- or beta-globulins or serum lipids. The information available at present is inadequate to determine the exact mechanism of disturbances in thermal coagulation point of blood serum.

SUMMARY

The thermal coagulation point of blood serum was correlated in 400 sera to total protein content of the serum, in forty-three cases to total albumins and globulins of the serum, in sixty cases to sedimentation rate and in 200 sera to the Weltmann heat flocculation test.

These data indicate that the thermal coagulation point of blood serum does not parallel the sedimentation rate nor the Weltmann reaction.

The data suggest that abnormal thermal coagulation of blood serum depends mainly upon quantitative and perhaps also qualitative disturbances in serum albumins, although the possible role of additional factors (alpha- and beta-globulins?) cannot be excluded as yet.

Because of the predominant role of albumins in influencing the thermal coagulation point of blood serum, the spectrum of positive results with this test in various diseases is different from that obtained with other serologic non-specific tests, thus affording a different type of diagnostic and prognostic information in disease.

REFERENCES

1. Huggins, C. Serum proteins in cancer. *Cancer Research*, 9: 321, 1949.
2. Huggins, C., Miller, G. M. and Jensen, E. V. Thermal coagulation of serum proteins. II. Deficient coagulation in cancer and the iodoacetate index. *Cancer Research*, 9: 177, 1949.
3. Black, M. M., Kleiner, I. S. and Bolker, H. Changes in the heat coagulation of plasma from cancer patients. *Cancer Research*, 8: 79, 1948.
4. Lecomte du Nouy. Studies in Biophysics: The Critical Temperature of Serum (56°C.). New York, 1945. Reinhold Publishing Corp.
5. Bauer, R. Mechanism of modern serum tests in relation to their clinical significance. Magnesium chloride, serum colloidal gold, cephalin-cholesterol, turbidity tests. *Rev. Gastroenterol.*, 16: 158, 1949.
6. Weltman, O. Über die Spiegelung exsudativ-entzündlicher und fibroser Vorgänge in Blutserum. *Med. Klin.*, 26: 240, 1930.
7. Halliburton, W. D. The proteids of serum. *J. Physiol.*, 5: 152, 1884; 7: 317, 1884.
8. Mellanby, J. H. The physical properties of horse serum. *J. Physiol.*, 35: 473, 1906–7.
9. Gutman, A. B. The Plasma Proteins in Disease. Advances in Protein Chemistry. Vol. IV, pp. 155–250. New York, 1948. Academic Press.
10. Schade, H. Kolloidchemie und Balneologie. *Med. Klin.*, 5: 1116, 1909.
11. Ehrentheil, O. and Weis-Ostborn, W. Ueber das verschiedene Verhalten des erhitzten Serums bei Carcinom und bei Anemia Perniciosa. *Klin. Wchnschr.*, 2: 585, 1923.
12. Belak, A. Ueber die Wirkung von Säuren auf den Zustand der Blutserumeiweisskörper. *Biochem. Ztschr.*, 90: 96, 1918.
13. Muller, W. Ueber die Hitzegerinnbarkeit des menschlichen Serums. *Ztschr. f. exper. Med.*, 55: 271, 1927.
14. Koopman, J. Over eenige physische eigenschappen van bloedserum van gezonden en zieken. *Nederl. tijdschr. v. geneesk.*, 67: 264, 1922.
15. Mayer, R. Ueber den Hitzekoagulationspunkt des Blutserums und seine Schwankungen. *Klin. Wchnschr.*, 1: 1693, 1922.
16. Rosenow, G. Ueber die klinische Verwertbarkeit der Serumhitzekoagulation. *Klin. Wchnschr.*, 1: 1694, 1922.

17. Hachez, E. Beitrag zur Serumhitzekoagulation des Blutes. (Untersuchungen bei Syphiliskranken.) *Klin. Wchnschr.*, 1: 2477, 1922.
18. Cossu, D. Sul punto di coagulazione al calore del siero di sangue e dei liquidi effusi. *Folia med.*, 10: 321, 1924.
19. Mayr, J. K. and Hofstadt, H. Lässt sich die Bestimmung des Hitzekoagulationspunktes in Blutserum differentialdiagnostisch verwerten. *München. med. Wchnschr.*, 71: 470, 1924.
20. Glass, Jerzy. Sur l'application de la récherche du point de coagulation thermique du serum sanguin pour l'évaluation clinique de divers états morbides ainsi que pour le diagnostic de certaines neoplasmes malignes. *Bull. internat. Acad. polon. d. Sc. et d. lett., Cl. med.*, pp. 935, Nov.–Dec., 1936.
21. Howe, P. E. The determination of proteins in blood —a micromethod. *J. Biol. Chem.*, 49: 109, 1921.
22. Robinson, H. W., Price, J. W. and Hogden, C. G. The estimation of albumin and globulin in blood serum. I. A study of the errors involved in the filtration procedure. *J. Biol. Chem.*, 120: 481, 1937.
23. Gutman, A. B., Moore, D. H., Gutman, E. B., McClellan, V. and Kabat, E. A. Fractionation of serum proteins in hyperproteinemia with special reference to multiple myeloma. *J. Clin. Investigation*, 20: 765, 1941.
24. Westergren, A., Theorell, H. and Widstroem, G. Plasmaeiweiss, Blutlipoide, Erythrocyten und Senkungsreaktion. *Ztschr. f. exper. Med.*, 75: 668, 1931.
25. Gray, S. J. and Mitchell, E. B. Effect of purified protein fractions on sedimentation rate of erythrocytes. *Proc. Soc. Exper. Biol. & Med.*, 51: 403, 1942.
26. Oakley, W. Erythrocyte sedimentation and the plasma fibrinogen. *Lancet*, 234: 312, 1938.
27. Hanger, F. M. Serological differentiation of obstructive from hepatogenous jaundice by flocculation of cephalin-cholesterol emulsion. *J. Clin. Investigation*, 18: 261, 1939.
28. Gray, S. J. The colloidal gold reaction of blood serum in diseases of the liver. *Arch. Int. Med.*, 65: 523, 1940.
29. Gray, S. J. and Barron, E. S. G. The electrophoretic analysis of the serum proteins in diseases of the liver. *J. Clin. Investigation*, 22: 191, 1943.
30. Kunkel, H. G., Ahrens, E. H., Jr. and Eisenmenger, W. J. Application of turbidimetric methods for estimation of gamma globulin and total lipid to the study of patients with liver disease. *Gastroenterology*, 11: 499, 1948.
31. Maher, F. T. and Mann, F. D. Turbidimetric estimation of serum colloids in extrahepatic disease. *Gastroenterology*, 12: 409, 1949.
32. Maher, F. T., Snell, A. B. and Mann, F. D. Turbidimetric estimation of serum colloids in differential diagnosis of hepatobiliary disease. *Gastroenterology*, 12: 394, 1949.
33. Kabat, E. A., Hanger, F. M., Moore, D. H. and Landow, H. The relation of cephalin flocculation and colloidal gold reactions to the serum proteins. *J. Clin. Investigation*, 22: 563, 1943.
34. Krebs, E. G. Depression of gamma globulin in hypoproteinemia due to malnutrition. *J. Lab. & Clin. Med.*, 31: 85, 1946.
35. Petermann, M. L. and Hogness, K. R. Electrophoretic studies on the plasma proteins of patients with neoplastic disease. I. Gastric cancer. *Cancer*, 1: 100, 1948.
36. Seibert, F. B., Pfaff, M. L. and Seibert, M. V. A serum polysaccharide in tuberculosis and carcinoma. *Arch. Biochem.*, 18: 279, 1948.
37. Shedlovsky, T. and Scudder, J. A. A comparison of erythrocyte sedimentation rates and electrophoretic patterns of normal and pathological human blood. *J. Exper. Med.*, 75: 119, 1942.
38. Longsworth, L. G. and MacInnes, D. A. An electrophoretic study of nephrotic sera and urine. *J. Exper. Med.*, 71: 77, 1940.
39. Bennhold, H., Kylin, E. and Rusznyak, S. Die Eiweisskoerper des Blutplasma. Steinkopf, 1938, Dresden.
40. Ariel, I. M., Rekers, P. E., Pack, G. T. and Rhoads, C. P. Metabolic studies in patients with cancer of the gastro-intestinal tract. x. Hypoproteinemia and anemia in patients with gastric cancer. *Ann. Surg.*, 118: 366, 1943.
41. Ariel, I. M., Abels, J. C., Pack, G. T. and Rhoads, C. P. Metabolic studies in patients with cancer of the gastro-intestinal tract. XI. Postoperative hypoproteinemia and relationship of serum protein fall to urinary nitrogen excretion. *Surg., Gynec. & Obst.*, 77: 16, 1943.
42. Jones, C. M. and Eaton, F. B. Postoperative nutritional edema. *Arch. Surg.*, 27: 159, 1933.
43. Moore, D. B., Pierson, P. S., Hanger, F. M. and Moore, D. H. Mechanism of the positive cephalin-cholesterol flocculation reaction in hepatitis. *J. Clin. Investigation*, 24: 292, 1945.
44. Recant, L., Chargaff, E. and Hanger, F. M. Comparison of the cephalin-cholesterol flocculation with the thymol turbidity test. *Proc. Soc. Exper. Biol. & Med.*, 60: 245, 1945.
45. Maclagan, N. F. The thymol turbidity test as an indicator of liver dysfunction. *Brit. J. Exper. Path.*, 25: 234, 1944.
46. Kunkel, H. G. and Hoagland, C. L. Mechanism and significance of the thymol turbidity test for liver disease. *J. Clin. Investigation*, 26: 1060, 1947.
47. Glass, G. B. Jerzy. Defective thermal coagulation of blood serum in cancer and other diseases and its clinical interpretation. *J. Mt. Sinai Hosp.*, in press.

Seminars on Cancer Research

Present Status of Clinical Cancer Chemotherapy*

DAVID A. KARNOFSKY, M.D. *and* JOSEPH H. BURCHENAL, M.D.
New York, New York

THE agents of value in the chemotherapy of cancer have been summarized and critically reviewed in a number of recent reports by Woglom,[1] Haddow,[2] Brues and Jacobson,[3] Karnofsky,[4,5] Gellhorn and Jones,[6] Shimkin and Bierman,[7] Clark,[8] Dodds[9] and Cade;[10] the most detailed clinical review, by Gellhorn and Jones,[6] appeared in this journal in February, 1949. In these articles the individual expressions of opinion as to the clinical applications of various agents to cancer therapy are in impressive agreement, and it is unnecessary to repeat the substance of these reports. We intend in this paper to examine the practical contributions that chemotherapy has made in the management of the patient with cancer. In doing this it will be necessary to explore the interrelationships in the clinical activity of the several chemotherapeutic agents and to compare their effectiveness with radiation therapy.

NATURE OF CANCER

To treat a disease rationally it is desirable to know as much as possible of the nature of the disease process. Much has been written about the nature of cancer, and some of the more plausible theories are presented in the preceding papers in this series. Although the various theories of cancer are of no immediate help to the therapist, a coherent view of the disease, whether ultimately correct or not, makes it easier to interpret the effects of various therapeutic agents.

A cancer may be regarded as a new organ which develops, grows and matures in a manner predetermined by its parent cells. In the neoplastic organ the cells are in various stages of differentiation, with stem cells and maturing forms. Some cancers may have a very complicated organization with cells at several morphologically evident levels of maturation. The opportunity to observe the natural evolution and possible decline of a tumor may be limited by the incidental lethal effect of the tumor on the host. Cancers show a more or less close relationship to their tissue or organ of origin so that they sometimes retain the functional properties of their normal analogues and they are partially dependent for their growth and integrity on the same factors as the normal tissues. It is thus possible to accelerate or depress the growth of some tumors by the same mechanisms which produce a similar effect on their normal analogues.

Tumors grow at various rates and they may infiltrate normal tissues and metastasize to other organs. The tumor cells stimulate the formation of a blood supply and a stromal reaction. There is no satisfactory evidence that an autologous host develops any defense against the extension of the tumor. The special stromal reactions present in some tumors may be due to the induction

* From the Chemotherapy Service, Memorial Hospital, and the Division of Experimental Chemotherapy, Sloan-Kettering Institute for Cancer Research, New York, N. Y. We wish to acknowledge with gratitude the aid of the American Cancer Society and the National Cancer Institute of the U. S. Public Health Service.

of such a tissue reaction by the tumor *per se* and not as a result of host defense.

Each tumor has its individual natural history which may be anticipated to some extent by its site of origin, histologic appearance, inherent rate of growth and the status of the host. It is likely that a tumor, as it follows its normal evolution, may become more resistant to x-rays or chemotherapy. It is difficult to prove that tumor cells inadequately treated at first by x-rays or chemotherapy are therefore more resistant to a further course of treatment. We are inclined to place the major emphasis for the development of tumor resistance to therapy on the maturation of the disease.

This descriptive hypothesis of cancer emphasizes the predetermined and individual course of the tumor in relation to a given host environment, its close physiologic relations in many cases to its tissue of origin, and the development of resistance to therapy as it progresses. This hypothesis does not answer the questions as to the immediate pathogenesis of cancer or the nature of the fundamental cellular abnormality which makes a tissue neoplastic, and these problems remained unsolved despite the enormous amount of work already completed and now in progress. In their solution we may expect to find a more satisfactory approach to the treatment of cancer.

CLINICAL STAGES OF CANCER THERAPY

The important stage in the treatment of cancer is the potentially curable one when prompt and adequate institution of treatment may completely eradicate the disease. Surgery and radiotherapy, by removing or destroying the cancer, are the best methods available for accomplishing this objective.

If the disease is too widespread for complete removal or if it has recurred extensively after previous therapy, the patient may still be greatly benefited by the use of *definitive palliative therapy*. In this stage the patient may be treated with methods which are known to produce clinical improvement and prolongation of useful life in a substantial number of cases. Radiation therapy and surgery are the chief methods of palliation but certain chemotherapeutic agents have proved themselves more effective in specific situations.

When the disease becomes widespread and unresponsive to definitive palliation and severe symptoms are present, the patient is ordinarily in the stage of far-advanced or terminal cancer. Chemotherapeutic agents may occasionally and in special instances produce a period of partial or temporary improvement in the disease or alleviate some of the distressing symptoms. The management of the patient with far-advanced cancer is a difficult one, and the indications for the trial of agents, which may be only occasionally and temporarily rewarding, may depend more on the sociologic and psychologic factors prevailing than on the hope of obtaining a substantial therapeutic response.

RADIATION THERAPY

Chemotherapy and radiotherapy often have closely related areas of activity in the treatment of cancer; the two methods are more or less effective in the treatment of certain stages of the disease and their proper combination in other situations may produce better results than exclusive dependence on either method alone. It is worth comparing the clinical effects and mechanism of action of these methods as a guide to their particular applicability to cancer problems. An enormous literature has developed in radiobiology and radiotherapy which can not be covered in a brief discussion; we are consequently including references to major source works on radiology.[11–19]

X-rays inhibit cellular proliferation, their effects varying with the total tissue dose, the rate of administration and the tissue treated. Affected cells may show mitotic inhibition and then recover or undergo early dissolution or survive for varying periods of time before dying. The effect of x-rays on cells appears to be a direct one although some tissue damage may result secondary to a damaged blood supply. The fundamental action of x-rays on susceptible

cells is not certain; there is good evidence that x-rays produce cellular injury indirectly by the formation of active radicals in water, which then react with the cell constituents, but they may also damage some important components of the cell by direct hits.[13,15,18]

The LD_{50} dose by total body irradiation, delivered at a single dose, ranges from 200 to 600r in several species of mammals; in man 350r seems to be a reasonable estimate of the LD_{50}. At the minimum lethal dose animals usually die within ten to twenty days or go on to gradual recovery. The lymphatic tissue, bone marrow, intestinal epithelium and gonads show the most striking histologic injury. In some mammals the intestinal injury appears to be most clearly related to the immediate cause of death whereas in man death from irradiation seems to be due principally to bone marrow aplasia, with the resultant leukopenia, anemia, purpura and generalized bleeding. The amount of x-rays that can be delivered to the entire body for therapeutic purposes is, therefore, limited by injury to bone marrow.

X-rays can be applied locally in large doses without producing severe systemic reactions, the total dose being limited by the size of the irradiated field and the particular area of the body treated. Tissue doses in the range of 2,000 to 4,000r, delivered over a period of two to three weeks or even longer, will produce severe and prolonged injury in skin, underlying tissues or in tumor tissues. By using several entry ports these or even higher doses of x-rays can be concentrated in a tumor-bearing area with the object of producing the maximum injury to the tumor tissue without causing serious and disabling effects in the adjacent normal tissue.

Both curative and palliative radiotherapy should be given according to a prearranged plan in doses adequate to accomplish one's objective.[20] The program for curative and palliative therapy may be very similar in practice although in the latter situation we know from experience that the disease will recur. If the effectiveness of radiation therapy could be improved even to a small degree by application of the newer knowledge in radiobiology or if the resistance of a tumor to x-rays could be reduced by nonradiologic methods, it might mean the difference between palliation and cure. This makes pertinent a consideration of some of the problems of radiotherapy, particularly as they are related to chemotherapy. Some of these problems are: method of x-ray dosage administration (dosage fractionation), the meaning of tumor sensitivity, the prediction of tumor sensitivity and the enhancement of the therapeutic activity of x-rays.

Dosage Fractionation. X-ray therapy is usually administered in fractionated doses over a period of several weeks. The fractionated form of therapy is believed to be easier on the patient; a larger dose of x-rays can be delivered to the tumor with less injury to normal tissue, acute and sometimes serious edematous reactions in the tumor are avoided, and the clinical results appear to be better.[11,21] The basis for dosage fractionation in clinical practice is not established and the systems of therapy are largely empirical. The cellular effects of x-ray are cumulative to a great extent but a given total dose is less injurious to both normal and neoplastic tissues as the over-all treatment time is prolonged. The total dose of x-rays applied must therefore be equated with both the total time over which the course of treatment was given and the time interval between successive fractions or successive courses. The chemotherapist has an interest in x-ray dosage fractionation because, experimentally, the basis for this procedure may be applicable to the use of some of his agents and, practically, some therapeutic problems can be best managed by the proper use of both x-rays and chemotherapeutic agents.

Tumor Sensitivity. The rate of tumor regression after a given dose of x-rays is not a true measure of curability. Tumors, depending on their origin, show different patterns of cellular degeneration after x-ray therapy

and the rapidly regressing tumors may also rapidly recur. In mice we have found that the single dose of x-rays which will destroy the transplantability of a wide variety of mouse tumors is fairly constant, in the range of 1,500 to 3,000r, although each tumor regresses at a different rate and shows an individual pattern of cellular injury.[22] A corollary of this point may be extracted from the important experiments of Jacobson and his group.[23] Rabbit bone marrow was made hyperplastic by the use of a hemolytic agent, phenylhydrazine. The rabbits were then exposed to a dose of x-rays which produced bone marrow aplasia in the control; in the phenylhydrazine-treated rabbits, however, the marrow remained cellular due to the persistence of stem cells and marrow recovery was consequently more rapid than in the controls. Ellinger[24] has discussed the problem of recovery from radiation effects and has stressed the importance of the regenerative capacity of the unaffected cells, and not the recovery of injured cells as the basis for tissue regrowth. It seems reasonable to suggest that tumors are composed to a greater or lesser extent of stem cells which are radioresistant, and the curative dose of x-rays necessary to destroy these cells may be in approximately the same range for all types of tumors. On the other hand, the rate of tumor regression, duration of the regression and rate of tumor regrowth in inadequately treated cases may reflect some of the special biologic properties of the tumor. From a curative point of view, radiosensitivity should mean radiocurability. In palliative therapy, however, production of rapid tumor regression may give considerable temporary relief and the term *radiosensitivity* in this situation has another and restricted meaning. The problem of radiosensitivity is of interest to the chemotherapist since he wishes to know if a given agent is acting on the growth manifestations of a tumor, or more fundamentally, in destroying the stem cells.

Prediction of Tumor Sensitivity. Tumor radiosensitivity may be an inherent characteristic of a given tumor and it may also bear a direct relationship to the radiosensitivity of the normal tissues of the host. Although tumors are usually treated uniformly according to location and type, it would be desirable to have a method for estimating the optimum therapeutic dose for each tumor and to appreciate which tumors will be unresponsive to x-ray therapy so that surgery can then be employed. Glucksmann[25,26] by the use of serial biopsies and Graham[27] by repeated cervical smears have studied this problem. Graham[27] has shown that early in the course of x-ray therapy to carcinoma of the cervix cytologic changes occur in the normal and neoplastic cells of the patients who will respond to x-rays (20/24 patients in Stage II and III were well during a brief follow-up period following x-ray therapy) whereas those not showing any cellular changes in the cervical smears responded poorly (only 2/28 patients in Stage II and III were free of disease during the follow-up period). It is possible that the so-called radioresistant patient would show a satisfactory response if higher doses of x-rays were given but this problem requires further study. If methods are developed for predicting those patients with carcinoma of the cervix in whom a given dose of x-rays will produce a high rate of cure, they may also be applied to other types of tumors. The chemotherapist is interested in the methods for estimating radiosusceptibility, both in reference to the possible use of these methods in evaluating the effectiveness of chemotherapeutic agents and as a means of determining the value of combining x-rays and chemotherapeutic agents in treating localized disease.

Enhancement of Radiation Effects. A number of agents have been reported to modify the lethal effects of x-rays in mice, including pretreatment with estrogens,[28,29] desoxycorticosterone,[30] cysteine,[31] horse serum,[28] pyridoxine[32] and folic acid.[32] Nitrogen mustard given prior to total body irradiation has been found to have an additive toxicity in mice whereas in the reverse sequence the effects are less than additive.[33] Mitchell[34,35] has reported, on the basis of

tissue culture experiments and clinical trials, that a synthetic vitamin K preparation (tetrasodium 2-methyl-1:4 naphthohydroquinone diphosphate) will enhance the effects of localized x-rays and its use causes a small but useful improvement in the palliative effects of x-rays.

The idea of selectively enhancing the effects of x-rays on a localized tumor or of selectively increasing the resistance of the normal tissues to x-rays is attractive and merits intensive study. The available evidence for such selective effects of systemic agents on tumor or normal tissues is not impressive. Satisfactory methods for obtaining a dynamic picture of the action of various agents on neoplastic and normal tissues are necessary in order to explore the value of combining x-rays and chemotherapy, and to determine the proper sequence of administration to obtain the optimal effect. The chemotherapist is greatly concerned with this problem because he may have agents whose proper use will result in a substantial improvement in the effectiveness of radiation therapy.

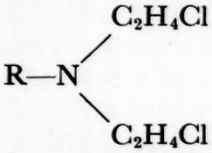
CLASSIFICATION OF CLINICALLY USEFUL AGENTS

The agents having an established role in the chemotherapy of human cancer may be classified as follows according to their probable mechanism of action on the tumor:[36] (1) agents acting as general cell poisons, i.e., nitrogen mustard, urethane, radioactive phosphorus and potassium arsenite; (2) agents acting as metabolic antagonists to substances essential to cell growth, i.e., folic acid antagonists; (3) agents injurious to specific cells, i.e., radioactive iodine and (4) agents changing the environment of hormonally dependent cells, i.e., estrogens and androgens.

General Cell Poisons

The agents in this group, while acting by different mechanisms, seem to interfere with cell division. Their effects are most striking on tissues undergoing rapid division, the lymphatic tissue, intestinal epithelium, bone marrow and testes. The fact that cells are rapidly dividing does not, *per se*, indicate that they are necessarily susceptible to these agents, but only tissues undergoing rapid division can show evidence of injury. The proliferation of some tumors is also inhibited by these agents, presumably by the same mechanisms affecting the normal tissues.

Nitrogen Mustard. The nitrogen mustards[37,38] are characterized by the formula



and the compound most frequently used clinically is methyl *bis* (β-chloroethyl) amine hydrochloride (HN2). A large number of derivatives of this molecule have been tested against mouse tumors and mouse leukemia[39,40] and several have been evaluated in man[41] but none seems to have any therapeutic advantage over HN2. Under physiologic conditions HN2 undergoes rapid intramolecular rearrangement with the loss of a chlorine ion to form a cyclic imine. This compound is highly reactive with a variety of chemicals and biologic substances such as vitamins, amino acids, nucleic acids and proteins. Nitrogen mustard is believed to exert its cellular effect by reacting with some nuclear component of the cell.[37]

On intravenous injection into animals HN2 is rapidly circulated throughout the tissues and is probably fixed there within a matter of one to two minutes. Animals receiving an LD_{50} dose of HN2 usually die in four to seven days or they show rapid recovery. The effects of the nitrogen mustards resemble in many respects those produced by x-rays;[42] thus sulfur and/or nitrogen mustard have been shown to produce mutations,[43] tumors in mice,[44] embryonic abnormalities[45] and a smaller degree of aplasia in rabbit bone marrow rendered hyperplastic by phenylhydrazine than in the normal marrow.[45] Thus x-rays and nitrogen mustards have a number of parallel effects on a variety of biologic

systems and on normal and neoplastic tissues.

The clinical effects of systemically administered HN2 resemble those of total body irradiation but certain important differences have become evident. These differences are diagrammatically shown in Figure 1. In reference to this figure it is noted that x-rays and HN2 act immediately on administration. The tissue damage produced by HN2 develops more rapidly but in animals or tissues surviving this injury recovery is much more rapid than in those treated with x-rays.

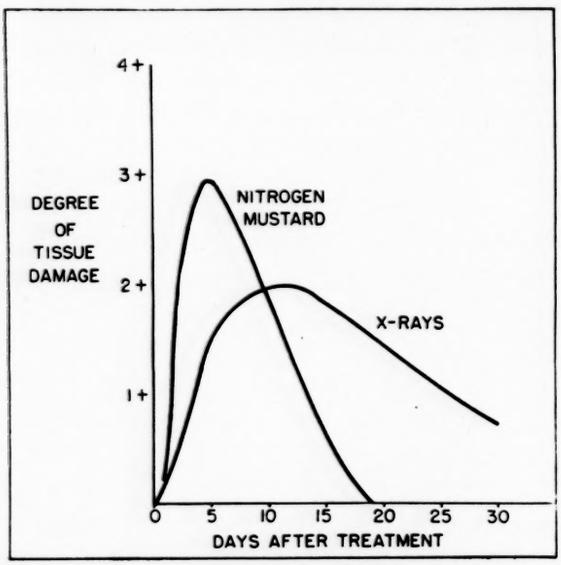


FIG. 1. A diagrammatic comparison of the tissue-damaging effects of clinically tolerated doses of nitrogen mustard and total body irradiation. (The plus signs are arbitrary representations of tissue injury and refer to no particular tissue or biologic system.)

If total body irradiation were given at a dose which produced the same degree of early tissue injury resulting from an LD_{50} dose of HN2, death would ultimately ensue; and, conversely, if the early tissue damage produced by an LD_{50} dose of x-rays were matched by a dose of HN2, only a transient effect would occur. We have estimated that the LD_{50} dose of HN2 by intravenous injection is 1.0 mg./kg. in man, and the LD_{50} dose of x-rays by total body irradiation is 350r. It can be simply calculated that the usual course of HN2 therapy, 0.4 mg./kg., is equivalent to about 140r of total body irradiation. From Figure 1 it is seen, however, that this comparison is not so simple in that the early therapeutic effect of 0.4 mg./kg. of HN2 may be equal to about 280r of total body irradiation, although the tissue recovery, both normal and neoplastic, is probably more rapid than that occurring after 100 to 150r of x-rays.

Two factors in clinical practice emphasize the more rapidly developing effects of HN2. A course of HN2 has usually been given over a four-day period but recently the trend has been, when safe, to give the course of treatment within one to two days;[38,47] thus the maximum effect of HN2 is quickly produced. X-ray therapy, and particularly total body irradiation, is applied in fractionated doses; by the Heublein technic the usual dose is about 16r per day, and a course of treatment, consisting of from 75 to 225r, requires five days to two weeks.[48] Secondly, HN2 has been given in relatively larger doses than total body irradiation. Thus it is common to produce a leukopenia of 1,000 or less following HN2 whereas, since the bone marrow depression may be more persistent after x-ray therapy, a depression of the white count to 3,000 usually has been an indication for the interruption of treatment.

A further conclusion from this analysis is that the susceptibility of cells to x-rays and nitrogen mustard is parallel. There is no evidence for the idea that tumor cells may be resistant to x-ray but responsive to HN2 or vice versa. It may be concluded that if tumor regression can be produced by systemically applied HN2, it could also have been accomplished if an equivalent dose of x-rays were applied to the proper area.

There are several advantages of HN2 over total body irradiation. These are as follows: (1) HN2 is inexpensive and may be easily administered. Nausea and vomiting usually follow each injection, however, and this may be temporarily distressing. (2) The therapeutic effects of HN2 appear rapidly; in most cases the nature of the therapeutic response will be indicated within two to

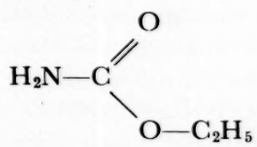
four days after treatment. (3) A larger initial therapeutic dose of HN2 may be given since the toxicity of the drug can be controlled more precisely than that of total body irradiation. (4) A course of HN2 is the best method of determining the continuing radiosensitivity of far-advanced lymphomas, particularly in widespread or occult disease. In a number of instances patients considered to be "radioresistant" have been salvaged for months (and, rarely, for longer periods) by a course of HN2. If the patient fails to show any response to a course of HN2, it is unlikely that he will respond to further x-ray therapy. In fact, the response to an adequate course of HN2 has been of prognostic value in the lymphomas and leukemia in that the longer the remission the greater is the likelihood that the patient will continue to show further response to HN2 or x-ray therapy. (5) HN2 has not produced the tumor edema which sometimes follows localized x-ray therapy. In tumors growing in vital areas, as in the thorax, a course of HN2 may cause immediate tumor regression and thus permit the safer application of x-rays.

HN2 has produced its most satisfactory results in extensive or "radioresistant" Hodgkin's disease.[49–58] It has been less consistently favorable in lymphosarcomas and mycosis fungoides,[59,60] has caused some palliation in inoperable carcinoma of the lung[61–63] and less often in other types of cancer. It is an effective but alternative form of treatment in chronic leukemia[64] and polycythemia vera.[49]

As with total body irradiation, the limiting factor in HN2 therapy is aplasia of the bone marrow. In most cases the marrow is moderately depressed by a course of HN2 but will recover within one month. As the disease progresses and particularly if bone marrow involvement develops, the patient may tolerate smaller doses of HN2 and the marrow may recover more slowly after each course of treatment. Vigorous therapy in this situation may induce a toxic HN2 reaction and lead to a severe and prolonged bone marrow depression.

HN2 is being used in combination with localized x-ray therapy in the treatment of inoperable carcinomas sufficiently circumscribed to justify a full course of radiation therapy. In our clinic a course of HN2 (0.4 mg./kg. intravenously) is given immediately preceding x-ray therapy to the local lesions. Tourniquets are applied to the upper thighs and one arm above systolic pressure during and for five minutes after the injection of HN2 in order to concentrate the action of HN2 centrally and perhaps to decrease the severity of the bone marrow depression by protecting the extremities. The full course of x-ray treatment is then delivered within a short period of four to six days. X-ray therapy directed to the local disease has not, in our experience, aggravated the leukopenia induced by HN2. The value of this combination therapy both as to its influence on the immediate symptomatic effects of irradiation therapy and in enhancing the therapeutic effects of localized x-rays is now under study.[65]

Urethane. Urethane or ethyl carbamate is a stable and relatively simple compound with the structure



It is of low toxicity in animals but in large doses will produce leukopenia[66] and decreased mitotic activity and cellular degeneration in the intestinal epithelium in mice, a fall in the reticulocyte count in rabbits,[67] leukopenia and thrombocytopenia in dogs,[68] lung tumors in mice and rats[69,70] and tumor regressions[71] and prolongation of life of mice with spontaneous and transmitted leukemia.[39,72,73] The urethane molecule is highly specific for these actions.[39,74] By the use of radioactive urethane, urethane was shown to be hydrolyzed in the body to carbon dioxide, ethyl alcohol and ammonia within twenty-four hours. This breakdown occurred more slowly in tumor-bearing than in normal mice.[75,76] It seems likely that urethane is concerned with nucleo-

protein synthesis, either acting as an antimetabolite or inhibiting certain enzymes involved in this process.

Clinically, the therapeutic total dose of urethane is in the range of 100 to 200 gm. with wide extremes on either side of these doses. Urethane is usually administered by mouth in a daily dose of 2 to 4 gm. Occasionally nausea and vomiting are prominent complaints and may prevent further treatment. In man excessive urethane therapy will produce leukopenia and thrombocytopenia which may be fatal.[77] The patient, therefore, should be observed carefully during treatment and the development of leukopenia will serve as an indication of impending toxicity. Urethane produces satisfactory remissions in chronic myelogenous leukemia and it is an alternative to other forms of therapy. It is not as generally effective in chronic lymphatic leukemia.[77–80] There has been no evidence of therapeutic specificity over other forms of therapy in these conditions. Its therapeutic activity in other types of cancer, with the exception of multiple myeloma, has been inconsistent and unpredictable.[81,82]

The work of Loge and Rundles[83] suggests that urethane may be of special value in the treatment of multiple myeloma. In a series of twenty-four patients recently reported[84] eight died before a satisfactory course of urethane was completed, fourteen had one or more courses with eight responding satisfactorily and two patients are still under treatment. In the successfully treated patients relief of pain, reversion of the bone marrow picture toward normal, a rise in hemoglobin and a decrease in abnormal serum proteins[85] occurred and the patients apparently showed a remission in the disease. Further work is necessary to determine the over-all frequency of remission and the effect of urethane on survival time in multiple myeloma. It is of interest that a significant number of objective remissions in multiple myeloma have not been reported with any frequency following nitrogen mustard, radioactive phosphorus or localized x-ray therapy. Stilbamidine has caused occasional relief of pain in multiple myeloma but has not altered the course of the disease.[86]

Radioactive Phosphorus. The effects of radioactive phosphorus have been studied intensively during the last ten years.[87–90] A detailed clinical evaluation has been presented recently by Lawrence and his group.[91–93] P^{32} liberates beta rays and has a half-life of fourteen days. It is concentrated in bone and in rapidly growing tissues. It exerts its effects largely through slow irradiation of the bone and bone marrow and in certain tumors showing a high level of cellular growth. It is usually given by mouth, the dose ranging from 5 to 10 mc. up to 25 mc. Since the irradiation from P^{32} is fairly slow, it may take one to two months before the maximum therapeutic or toxic effects develop. Excessive doses will produce bone marrow aplasia which may lead to leukopenia, thrombocytopenia, bleeding and death.

It is generally agreed that the chief value of P^{32} is in the treatment of chronic leukemia in which it is an alternative form of treatment, and in polycythemia vera in which it appears to be the treatment of choice. It has not proved to be very useful in the treatment of the lymphomas, multiple myeloma or acute leukemia.

Potassium Arsenite. This agent, as Fowler's solution, has been widely used in the treatment of chronic myelogenous leukemia.[94] It has produced satisfactory remissions but there have been no extensive clinical reports on its use. It may be regarded as one of the alternative methods for the treatment of chronic myelogenous leukemia.

Metabolic Antagonists

It has frequently been suggested that if cancer cells could be shown to have a unique metabolic requirement or excessively high requirement for a physiologic compound, antagonists might be prepared which would interfere with the utilization of these substances. Burchenal et al.[95] found that 2,6-diaminopurine, an adenine antagonist, would prolong the life of leukemic

mice. Kidder et al.[96] have inhibited the growth of mouse mammary carcinoma E0771 with 8-azoguanine, a guanine antagonist. Azoguanine has not shown any therapeutic effects clinically[97] and the activity of 2,6-diaminopurine has been inconsistent in acute leukemia.[98] In a preliminary clinical trial desoxypyridoxine, a vitamin B_6 antagonist, failed to show any effect on lymphosarcoma or acute leukemia.[99] Thus far, only the 4-amino derivatives of folic acid, which are very effective folic acid antagonists,[100,101] have been found of value in the treatment of acute leukemia, particularly in children.[102,103]

4-amino Derivatives of Folic Acid. The 4-amino derivatives of folic acid have an NH_2 group substituted for the hydroxyl group on the 4-position of the pteridine nucleus of folic acid. This seemingly minor change has produced a compound of extraordinary toxicity which will induce acute folic acid deficiency in animals and man. Folic acid is essential for the growth of some cells, presumably because of its role in purine metabolism. The evidences of acute folic acid deficiency, as produced by 4-amino PGA, include interruption in the growth of certain tissues, embryonic[104] and estrogen-dependent tissues,[105] and of the bone marrow and intestinal epithelium in intoxicated animals.[106] The survival of mice with transplanted leukemia is prolonged by treatment with 4-amino PGA[107] and the growth of solid tumors is inhibited.[108–110] The growth-inhibiting effects of 4-amino PGA on mouse tumors, leukemia and on normal tissues may be prevented within narrow dosage limits by large amounts of folic acid.[111] Although the toxicity of the various 4-amino derivatives of folic acid differs quantitatively, at equivalent pharmacologic doses the induced toxicologic pictures are similar.

The 4-amino folic acid antagonists apparently act over an appreciable period after their introduction into the body. Their action is presumed to be direct since evisceration and nephrectomy, and adrenalectomy do not interfere with their action on the intestinal epithelium and bone marrow. The toxicity of 4-amino PGA to these tissues is increased approximately three- to fourfold by bilateral nephrectomy in rats.[112] In keeping with the view that the continuing concentration of the 4-amino, antagonist is important in its action, 4-amino PGA or 4-amino N^{10} methyl PGA has been shown to be more toxic if a given total dose is fractionated over a period of several days instead of being given in a single dose.[106]

The most satisfactory folic acid antagonist for clinical use in our experience is 4-amino N^{10} methyl PGA (A-methopterin). In man the tolerated dosage varies remarkably from patient to patient. It must be given cautiously and treatment followed with frequent blood studies. The signs of toxicity are oral ulcerations, leukopenia, aplasia of the bone marrow, thrombocytopenia, bleeding, intestinal pain, diarrhea and bleeding, cutaneous eruptions, increased susceptibility to infection and alopecia. The appearance of these signs is an indication for decreasing the dosage or temporarily stopping the treatment. 4-amino N^{10} methyl PGA is usually given by mouth or intramuscularly, and the initial dose is 2 to 5 mg. in childrens and 5 to 10 mg. in adults. Renal or hepatic insufficiency seems to increase the toxicity of the drug. The principle of therapy is to continue the drug and increase the dose cautiously until clinical improvement or signs of toxicity develop. If toxicity appears first, the treatment is stopped until the toxic complications subside when therapy is resumed at a lower dose.

The folic acid antagonists have produced repeated temporary remissions in 20 to 30 per cent of the patients with acute leukemia. Ultimately the disease may be expected to become refractory to treatment although there is no doubt that in favorable cases life is prolonged for as yet undetermined periods.[98,102,113–116] The leukemic process appears to become more resistant to the induced folic acid deficiency and finally proceeds unaffected in spite of vigorous therapy. Resistance to the folic acid antagonists, possibly similar to the clinical

situation, has been developed in transplantable mouse leukemia.[117] Lymphosarcoma in children may occasionally show a very satisfactory temporary response but in adults tumor regressions have been associated only with evidences of toxicity. Chronic myelogenous leukemia shows a transient remission to 4-amino PGA and relapse occurs promptly after the cessation of therapy.[118] A variety of other types of tumor have failed to show a consistent or satisfactory response to treatment with the folic acid antagonists.

Agents Injurious to Specific Cells

The discovery of toxic substances which would selectively concentrate in tumor cells or certain types of tumors is one of the most promising approaches to cancer chemotherapy. If a non-toxic agent were selectively concentrated, it could be rendered injurious to the cells by making it radioactive. Thus far only radioactive iodine has been shown to be of clinical value.[119–124]

Radioactive Iodine. The normal thyroid gland selectively concentrates iodine and a small number of thyroid carcinomas will retain this property. If radioactive iodine is used, it will also concentrate in the functionally active thyroid tissue; and if a large dose is given, it will produce severe radiation damage to the active thyroid tissue. Such large doses of I^{131} (200 to 300 mc.) may also damage the bone marrow, probably the limiting factor in treatment.

The problem in treating thyroid cancer is to concentrate the maximum amount of I^{131} in the neoplastic tissue. It is estimated that only about 15 per cent of thyroid carcinomas, principally the follicular adenocarcinomas and the metastasizing strumas, take up an appreciable amount of radioactive iodine,[120,121] as can be determined by tracer doses of I^{131}. Only about 3 to 5 per cent of the thyroid tumors take up iodine in sufficient amount to obtain a therapeutic effect. The uptake of I^{131} in the tumor may be increased by eliminating the normal thyroid, preferably by surgery, or by the use of a preliminary dose of I^{131}. The use of thiouracil prior to I^{131} may also increase the iodine uptake.[124] Thus far I^{131} has produced remarkable clinical improvement in a small group of cases but there has been no definite proof of cure of these patients.

Hormonal Alterations

Certain organs are dependent on hormones for their growth, function and morphologic integrity; the prostate and mammary glands are prime examples. By producing changes in the hormonal balance of the body these organs may show marked changes in appearance and function. Carcinomas arising from these organs often retain some of the hormonal dependencies of their normal analogues for varying periods during the course of the disease although they finally seem to become hormonally independent. Hormonal alterations can be readily produced in males and females by castration or by the administration of androgens or estrogens. Further attempts to change the hormonal balance by the use of other steroids or decreasing or altering pituitary or adrenal function are now being made but have not yet proved of clinical value.

About 50 to 75 per cent of carcinomas of the prostate are partially dependent on androgens for continued growth. By orchidectomy or administration of estrogens tumor regression and associated evidences of clinical improvement occur in these cases.[125–127] The treatment is usually effective for one to two years but the disease then recurs in a hormonally resistant form. Hormonal therapy is now the accepted method for the temporary control of inoperable prostatic carcinoma. Carcinoma of the male breast also shows a remarkable temporary response to castration.[128]

The value of hormonal alterations in inoperable cancer of the breast in women is not as well established as in prostatic carcinoma.[129–132] Castration, estrogens, androgens or the withdrawal of hormonal therapy in patients unresponsive or unsuitable for x-ray treatment has, in an appreciable number of cases with inoperable

and far-advanced disease, produced objective and subjective improvement. (Table 1.) These effects consist of regression of soft tissue lesions, recalcification of osseous metastases, temporary interruption in the spread of the disease, relief of pain and reserved for the patient with inoperable breast cancer, unsuitable for or no longer responsive to x-ray therapy or castration.[131] This form of treatment may become more useful when we can understand the nature, production and control of hormonal im-

TABLE 1

TENTATIVE INDICATIONS FOR THE USE OF ESTROGENS AND ANDROGENS IN TREATMENT OF INOPERABLE MAMMARY CARCINOMA[129–132]

Compounds Used and Dosage	Age of Patient	Treatment Period before Improvement	Objective Improvement	Subjective Improvement	Duration of Improvement
Estrogens					
Orally (daily): Diethylstilbestrol, 5 mg. t.i.d. Ethinylestradiol 1 mg. t.i.d. Sodium estrone sulfate, 10 mg. t.i.d. Intramuscularly (3 × weekly): Estradiol benzoate, 5 mg.	10 yr. postmenopausal or over 60 yr. of age	Range 2 wk. to 7 mo., usually 2 to 5 mo.; highest percentage of improvement has occurred after total of 1 gm. or more of diethylstilbestrol or its equivalent	40–50% show regression soft tissue and skin tumors; older patients seem to be more favorably affected; osseous lesions may also show recalcification	60% show relief of pain, increase in general activity	Range has been 1 to 22 mo., with 50% of patients with objective improvement continuing in half the patients for 7 mo. or longer
Androgens					
Intramuscularly (3 × weekly): Testosterone propionate, 100 mg.	Premenopausal to 10 yr. or more postmenopausal	Range 2 wk. to 11 mo., usually 2 to 5 mo.; highest percentage of improvement has occurred after total dose of 3 gm. or more	20% of osseous lesions may show evidence of recalcification; 25% of soft tissue tumors have also improved	70% show relief of pain, increase in general activity	Range has been 1–45 mo., with average of about 6 mo.

increase in well-being and ability to carry on normal activities. In some cases, particularly those in which estrogens have been used in premenopausal patients, the course of the disease seems to have been accelerated. Hormonal therapy may often produce unpleasant side reactions. Estrogens may cause salt and water retention with peripheral edema which sometimes leads to heart failure, nausea and vomiting, painful and enlarged breasts, uterine bleeding, diarrhea and hypercalcemia in patients with osseous metastases; androgens may cause water retention and hypercalcemia and also evidences of masculinization with hirsutism, lower pitch of voice, increased libido and amenorrhea.

Hormonal therapy should therefore be balances and the hormonal imbalance which will prove most effective against each type of tumor. It is regrettable that nothing comparable to the acid phosphatase determination in prostatic cancer is known to serve as an objective measure of the effect of hormonal treatment on mammary cancer. Certain arbitrary indications for hormone treatment based on the best available information have been suggested.[131,132] Estrogens are used only in women five to ten years postmenopausal or over sixty years of age, and androgens are used in all other cases. In some situations, when prolonged hormonal therapy is no longer effective, withdrawal has produced clinical improvement.[130] The tentative indications for therapy are summarized in Table 1.

PRESENT STATUS OF CHEMOTHERAPY IN TREATMENT OF INOPERABLE CANCER

The tremendous interest in the chemotherapy of cancer is out of proportion to the practical contributions that chemotherapy thus far has made to the management of the disease. This interest is entirely justified, however, because chemotherapy, in principle, offers the best hope of controlling cancer, the various aspects of chemotherapeutic research represent a cross section of modern science, and the clinical material available for study offers an endless variety of fascinating problems. In order to summarize what has been accomplished, the indications for specific chemotherapy and the results to be expected in the various sites and types of neoplastic disease are summarized in Tables II and III. The footnotes in each table explain the method of presentation.

Chemotherapeutic agents have been found to show some regular activity in four sites of carcinoma. In *inoperable carcinoma of the prostate* castration or estrogen therapy is the primary method of palliation. Fifty to 75 per cent of the patients respond well to androgen control therapy. Relief of symptoms following castration usually occurs within thirty-six hours whereas improvement with estrogen therapy may not appear for seven to ten days. The end results of both methods of treatment are approximately the same, although in rare instances when the castrated patient begins to relapse estrogenic hormone may cause another period of improvement and vice versa. Hormone therapy produces remarkable clinical improvement during the major part of the patient's life, and life has been prolonged for long periods in many cases. The average increase in survival, however, is about six to twenty-four months.[6] When the patient becomes refractory to hormonal therapy, secondary palliative measures such as nitrogen mustard,[63] urethane[81,82] or x-ray therapy are of uncertain and transient value in relieving pain.

In the occasional *metastatic thyroid carcinomas* which can be induced to concentrate an appreciable amount of iodine, radioactive iodine appears to be an important primary method of palliation. In these selected cases objective and subjective improvement is marked and life may be appreciably prolonged.[123,124] It is too early to predict the end results of I^{131} therapy or its ultimate applicability in thyroid cancer.

Radiation therapy is the primary method of palliation in *inoperable breast cancer*. When the disease is widespread, estrogen therapy in the patient over sixty years of age or five to ten years postmenopausal, and castration and/or androgen therapy in the other patients is a secondary method of palliation. The results to be expected from hormonal therapy are summarized in Table I. The activity and sense of well-being of the patients responding to hormonal therapy are greatly increased although there is no clear evidence that life is, in general, appreciably prolonged.

Radiation therapy is the principle technic for controlling *inoperable carcinoma of the lung*. It may successfully control the local disease. Death is usually due to metastatic spread. When significant symptoms are present and radiation therapy is not indicated, nitrogen mustard has induced symptomatic relief for periods of two to twelve weeks (average five weeks) in 60 to 65 per cent of the patients, and objective improvement has been observed in 40 to 45 per cent.[61–63] This improvement has been particularly striking in patients with anaplastic bronchogenic carcinoma with obstruction of the superior vena cava. As the disease progresses, it becomes less responsive to repeated courses of nitrogen mustard; but some patients have remained relatively comfortable on this form of therapy for a year or longer. There is no evidence that nitrogen mustard therapy, in general, has appreciably prolonged life.

Nitrogen mustard has on rare occasions served as a palliative measure in other types of neoplastic disease.[63] The beneficial effects have been so unpredictable, however, that a course of HN2 cannot be recommended as a general secondary palliative procedure.

As shown in Table II no palliative chemotherapeutic procedures can be advocated for some of the major types of inoperable cancer.

The chemotherapeutic agents have acquired important functions, approaching those of radiation therapy, in the treatment of the lymphomas, leukemia and allied diseases. (Table III.) In acute leukemia, the 4-amino folic acid antagonists (aminopterin, A-methopterin, etc.) have produced temporary hematologic remissions and clini-

TABLE II

PRESENT STATUS OF CHEMOTHERAPY IN TREATMENT OF INOPERABLE CARCINOMAS AND SARCOMA*

Site†	Cancer Deaths, U.S.A., 1946‡ (all ages)			Primary Palliation§	Secondary Palliation‖
	Total	Male	Female		
Intestines (lower bowel)	32,239	15,847	16,392	Surgery	
Stomach	25,625	15,984	9,641	Surgery	
Miscellaneous abdominal organs	19,695	9,695	10,000	Surgery	
Breast	17,516	242	17,274	Radiotherapy; surgery	*Hormone therapy:* (See Table I) *androgens* *estrogens* Castration
Uterus	17,205		17,205	Radiotherapy; surgery	
Lung	12,706	9,877	2,829	Radiotherapy; surgery	*Nitrogen mustard*
Prostate	10,616	10,616		*Androgen control therapy; estrogens;* castration	Radiotherapy
Miscellaneous and unspecified sites	10,211	5,395	4,815		
Urinary bladder	5,746	3,755	1,991	Radiotherapy; surgery	
Buccal cavity and pharynx	5,438	4,305	1,133	Radiotherapy; surgery	
Ovary	4,669		4,669	Radiotherapy	
Skin	3,520	2,115	1,405	Radiotherapy; surgery	
Esophagus	3,307	2,629	678	Radiotherapy; surgery	
Central nervous system	3,168	1,873	1,295	Radiotherapy; surgery	
Kidney	2,900	1,817	1,083	Radiotherapy; surgery	
Upper respiratory tract; miscellaneous	2,510	2,106	404	Radiotherapy; surgery	
Bone	2,308	1,246	1,062	Radiotherapy; surgery	
Male genital tract; miscellaneous	948	948		Radiotherapy; surgery	
Female genital tract; miscellaneous	772		772	Radiotherapy; surgery	
Thyroid gland	728	232	496	Radiotherapy; *radioactive iodine*	
Adrenal gland	178	118	60	Radiotherapy; surgery	
Total	182,005	88,801	93,204		

* We are grateful for the assistance and, particularly, the advice of the Statistical Research Section of the American Cancer Society in the preparation of Tables II, III and IV. (The chemotherapeutic indications for specific conditions are italicized. The roles of radiotherapy and surgery in relation to chemotherapy are also indicated.)

† The classification of cancer sites is that used by the National Office of Vital Statistics.

‡ The cancer death rate is based on the Vital Statistics of the United States, 1946. Part I. Federal Security Agency, Public Health Service, National Office of Vital Statistics, U.S. Printing Office, Washington, D.C. The death rate serves as an arbitrary method of estimating the number of new patients each year who would probably require palliative therapy; the death rate does not indicate the total number of patients receiving palliative therapy during a given year since some patients respond to treatment, even in the far-advanced stages of their disease, for more than one year.

§ Primary palliation refers to the use of specific methods or surgical procedures which are likely to produce palliation in certain clinical situations.

‖ Secondary palliation refers to methods of therapy reserved for the patient with far-advanced cancer (unsuitable or refractory to primary palliation) which sometimes produce a limited period of improvement. In occasional patients procedures listed under primary and secondary palliative procedures have been used at the same time. This type of classification is, therefore, not a rigid one.

cal improvement in an appreciable number of cases, ranging from 25 to 30 per cent, and each remission usually lasts about six to eight weeks, although some have continued for longer than four months.[98,102,113–116] Although these agents are of limited value, they are the treatment of choice in acute leukemia, particularly in children. The folic acid antagonists should be started as soon as the diagnosis of acute leukemia is established. The drug is administered until evidence of a hematologic remission or toxicity appears; if the latter occurs first, the drug is temporarily discontinued or it is administered in a lower dose. During the treatment period the patient is supported by blood transfusions and antibiotics as indicated. When a hematologic remission occurs, treatment is stopped although the patient is followed with frequent bone marrow studies so that the drug can be restarted at the earliest sign of hematologic relapse. Repeated remissions have been produced in the responsive patients and there can be no doubt that life has been prolonged for an as yet undetermined period in this selected group. The 4-amino anti-folics have not produced as high a remission rate in acute leukemia in the adult,[98] and patients in the terminal stage of chronic myelogenous leukemia have not shown any improvement. Against the previous background of our inability to modify the course of acute leukemia the folic acid antagonists represent a significant therapeutic advance.

Satisfactory remissions may be produced in chronic myelogenous leukemia by means of x-ray therapy,[134] radioactive phosphorus,[88,89,91] nitrogen mustard,[41,64] urethane[78,79] or potassium arsenite.[94] Early in the disease these agents all seem to be effective, but as the disease advances the remissions become shorter and less satisfactory. The proper method of managing the disease depends to a large extent on the experience and preference of the physician. X-ray therapy to the spleen is probably the simplest and most satisfactory method of treating the early disease.[134] Radioactive phosphorus has also induced excellent clinical remissions although its availability is limited. Nitrogen mustard will induce a rapid clinical remission in suitable cases since the dosage can be fairly well controlled. However, nausea and vomiting during treatment may be distressing and the remissions seem to be shorter than those following x-ray therapy.[64] Some patients can be maintained satisfactorily by periodic injections of HN2.[53] Urethane or Fowler's solution is administered orally over a period of one to six weeks before evidence of clinical improvement appears. Because of their unpleasant side effects and less satisfactory dosage schedule these agents are not generally used in our clinic. Although there is a natural tendency to shift from one method of therapy to another as the patient enters the terminal stage of the disease, one does

TABLE III

PRESENT STATUS OF CHEMOTHERAPY IN TREATMENT OF LEUKEMIA, LYMPHOMAS AND ALLIED DISEASES*

Type	Estimated Deaths per Year, U.S.A. (all ages)			Therapeutic Procedures
	Total	Male	Female	
Acute leukemia	cā 2,000			*Folic acid antagonists*
Chronic myelogenous leukemia	2,245	1,205	1,040	Radiotherapy; *radioactive phosphorus; nitrogen mustard; urethane; potassium arsenite*
Chronic lymphatic leukemia	2,480	1,440	1,040	Radiotherapy; *radioactive phosphorus; nitrogen mustard*
Monocytic leukemia	190	135	55	*Folic acid antagonists; nitrogen mustard;* radiotherapy
Lymphosarcoma (all types)	2,830	1,680	1,150	Radiotherapy; *nitrogen mustard*
Hodgkin's disease	3,420	1,960	1,460	Radiotherapy; *nitrogen mustard*
Mycosis fungoides	cā 150			Radiotherapy; *nitrogen mustard*
Multiple myeloma	ca 200			Radiotherapy; *urethane*
Polycythemia vera	Not estimated			*Radioactive phosphorus;* radiotherapy; *nitrogen mustard*
Total	13,510			

* This table includes the so-called systemic diseases. These diseases are not all specifically classified in the Vital Statistics figures for 1946, and some of the deaths in this table are also included in Table II. Because of the importance of chemotherapy in these diseases we have estimated the probable yearly death rates for these conditions. (The annual death rates for these conditions are estimated from the Connecticut cancer incidence figures[133] and the Vital Statistics of the United States, 1946. The estimates are not the products of a documented analysis.)

not often see one type of therapy succeed when adequate trial of another has failed. If the patient is in poor general condition when first seen, a course of nitrogen mustard may be the quickest method of bringing the disease under control or establishing whether it will or will not be responsive to treatment. If the patient shows no improvement after a course of nitrogen mustard, it is unlikely that the other agents will be of value. The average survival time in leukemia is probably increased by only a few months by the present forms of therapy,[135,136] and the purposes of palliative therapy are to keep the patient in good general condition and to permit him to lead a normal life for as long as possible during the course of his disease.

Chronic lymphatic leukemia requires more conservative management than chronic myelogenous leukemia since the response to therapy is more variable; and if treatment is pushed intensely, it may do more harm than good.[64] Many patients may be maintained by a minimum of therapy and blood transfusions as needed. X-ray therapy and radioactive phosphorus have given long periods of clinical improvement;[88,92] either one of these methods is satisfactory for managing the disease. Urethane and nitrogen mustard have produced clinical and hematologic improvement in some cases but the seemingly unpredictable occurrence of toxic effects has made their general use hazardous, in our experience.[64,79] If these latter agents are used, they should be given with considerable caution.

The treatment of monocytic leukemia cannot be specifically defined. X-ray therapy, nitrogen mustard[64] and the folic acid antagonists,[137] although they have failed in most instances, have been associated with periods of clinical improvement in some cases.

Perhaps more clearly than in any other condition the response of inoperable lymphosarcoma to therapy can be correlated with the natural course of the disease. The slowly growing process may be present for long periods and bulky tumors may exist without seriously interfering with the patient's activity. X-ray therapy in these patients will produce tumor regression and marked clinical improvement for long periods of time. At the other extreme is the highly aggressive lymphosarcoma, in which x-ray therapy or nitrogen mustard will produce only a transient regression in tumor growth. X-ray therapy is the treatment of choice in lymphosarcoma. When the disease is far-advanced and too extensive for further x-ray therapy, nitrogen mustard has proved effective (temporarily) in only 10 to 20 per cent of the cases. HN2 should be administered cautiously since these patients may show a toxic reaction to an ordinary course of therapy. In the more slowly progressing types of lymphosarcoma life has been appreciably and satisfactorily prolonged by active therapy.

X-ray therapy is the preferred method of treating Hodgkin's disease.[38,57,135] In the patients with generalized disease and with systemic symptoms not controlled by x-ray therapy to tumor-bearing areas, nitrogen mustard therapy is indicated. A good response to HN2, as evidenced by a regression in the lymph nodes, spleen and liver, disappearance of fever, relief of pruritus and increase in strength and appetite, may occur in 50 to 90 per cent of the patients, depending on the stage of the disease. The average duration of remission is about four to eight weeks, and the longer the remission the more satisfactory the response to further HN2 or x-ray therapy. There is ample evidence that some patients have been salvaged for several months or longer by HN2 although the course of the disease in general has not been altered.[49–56,58,138–142] A successful response to HN2 may permit the further use of x-ray therapy to localized areas of disease. In the terminal stage of the disease leukopenia and anemia may develop, and these may be aggravated by nitrogen mustard therapy;[143] however, although the risk may be considerable, the presence of leukopenia does not contraindicate the cautious use of nitrogen mustard.

Mycosis fungoides, disseminated and not responding satisfactorily to x-ray therapy,

may show improvement for several months or longer following HN2 therapy, which is indicated in these cases.[59,60] Usually, however, far-advanced cases of mycosis fungoides show internal evidence of lymphosarcoma and the response to nitrogen mustard has been very transient.

X-rays will sometimes control the local manifestations of multiple myeloma.[144] The observations of Loge and Rundles[83] on the production of clinical and hematologic remissions with urethane await confirmation before urethane can be recommended for the treatment of all cases. Stilbamidine[86] and nitrogen mustard[63] have given some relief of pain but they have not altered the course of the disease.

The management of polycythemia vera is chiefly a problem in selecting the safest and most convenient of a long list of agents including radioactive phosphorus, nitrogen mustard, x-ray therapy and phenylhydrazine, or the use of venesection. Although radioactive phosphorus is regarded by many as the treatment of choice,[93] it has been suggested that patients receiving P^{32} may show an increase in the incidence of acute leukemia.[145] Nitrogen mustard produces satisfactory remissions[146] but they are shorter in duration than those produced by P^{32} or x-rays. There is good evidence that treatment will relieve symptoms, reduce complications and prolong life.

Neoplastic disease in children occupies an important place in the cancer problem since it is the third most frequent cause of death in children between the ages of three and ten years.[147] Acute leukemia, which represents about 40 to 45 per cent of the neoplastic disease in children (Table IV), is temporarily improved and life prolonged in 25 to 30 per cent of the cases with the 4-amino folic acid antagonists. In the rarer cases of chronic leukemias in children nitrogen mustard and urethane have produced brief clinical remissions. Lymphosarcoma often responds to nitrogen mustard with rapid tumor regression although the improvement may last for only two or three weeks. In about 25 per cent of the cases the 4-amino folic acid antagonists will also cause lymphosarcoma to regress, sometimes for as long as two to three months. Thus the nitrogen mustards may be used to produce immediate symptomatic relief, and the folic acid antagonists may then be given with the possibility of causing a more prolonged remission.

TABLE IV
PRESENT STATUS OF CHEMOTHERAPY IN TREATMENT OF INOPERABLE NEOPLASTIC DISEASE IN CHILDREN (0–15 YEARS)*

Site	Cancer Deaths, U.S.A., 1946† (0–15 yr.)			Therapeutic Procedures
	Total	Male	Female	
Leukemia†	1,152	665	487	*Folic acid antagonists; nitrogen mustard; urethane*
Central nervous system	414	225	189	Surgery; radiotherapy
Urinary tract	227	124	103	Radiotherapy; surgery
Digestive tract and abdominal organs	160	95	65	Radiotherapy; surgery
Bone	136	66	70	Radiotherapy; surgery
Hodgkin's disease	82	54	28	Radiotherapy; *nitrogen mustard*
Miscellaneous and unspecified	427	234	193	
Total	2,598	1,463	1,135	

* The deaths in this table are also included in Tables II and III but because of the interest in cancer in children the figures are presented separately.

† This group presumably includes lymphosarcoma.

The other types of tumors in children have not responded consistently to chemotherapy although nitrogen mustard occasionally has produced a regression in neuroblastomas and in Wilms' tumor. The use of the combination of HN2 and x-rays in these tumors is now under investigation. The reticuloendothelioses may sometimes respond to HN2 and to the 4-amino folic acid antagonists;[148] further study in these conditions is indicated.

Important concomitants to the chemotherapy of cancer, particularly in far-advanced cases, are supportive measures such as the antibiotics and blood transfusions, careful attention to the patient's symptomatic complaints and the creation of a hopeful atmosphere. These general measures may in many instances be more

important to the patient's well-being and survival than the specific chemotherapeutic agents applied.

CLINICAL INVESTIGATIONS IN CANCER CHEMOTHERAPY

Intensive laboratory and clinical investigations of chemotherapeutic agents are in progress and a vast amount of information is being accumulated on their mechanism of action *in vitro* and *in vivo*, their therapeutic interrelationships and their effects on a wide variety of tumors. These studies, besides contributing new ideas, will provide the experience and facilities for the clinical evaluation of newly proposed methods of therapy.

The agents now being used in the experimental treatment of cancer may prove to be of importance although their clinical value has not yet been established. The relation of the pituitary-adrenal system to cancer is now being investigated with renewed intensity. Dobriner, Lieberman and Rhoads[149–152] examined the metabolism of the adrenal steroids in normal and cancer patients and they observed the presence of an abnormal urinary steroid pattern in many patients with neoplastic disease. With the recent availability of the adrenocorticotropic hormone (ACTH) and cortisone (11-dehydro-17-hydroxycorticosterone) for clinical use these agents are now being tested for their therapeutic and metabolic effects on several types of cancer. In a preliminary study[153] ACTH was reported to produce regressions in lymphomatous diseases including lymphatic leukemia although in several cases the tumors recurred within a short period after the cessation of treatment. Single patients with carcinoma of the prostate and breast failed to respond. Further studies are being pursued on a wider spectrum of tumor types, with the use of ACTH, cortisone and other steroid compounds.

The long list of radioactive isotopes, in their inorganic forms or incorporated into organic molecules, are being tested for their therapeutic activity in patients with cancer.[154,155] Recent clinical reports include studies on radioactive arsenic[156] and sodium[157] and a survey of radioactive gallium is in progress.[158]

The attempt to control tumors by the selective localization of cancerotropic viruses has been under laboratory study.[154,160] Hoster et al.[16] have suggested that viral hepatitis might possibly have a beneficial effect on Hodgkin's disease and they have issued a preliminary report on a group of patients experimentally inoculated with the virus.

These problems are illustrative and represent only a fraction of the numerous clinical studies now in progress in cancer chemotherapy[2,5–7,162] The wide sweep of this extensive clinical activity is illuminating all aspects of the cancer problem and it can only lead to an acceleration in our progress toward the goal of controlling neoplastic growth.

REFERENCES

1. Woglom, W. H. General review of cancer chemotherapy. In Approaches to Tumor Chemotherapy. P. 1, Am. A. Advance. Science, 1947.
2. Haddow, A. Note on the chemotherapy of cancer. *Brit. M. Bull.*, 4: 417, 1947.
3. Brues, A. M. and Jacobson, L. O. Comparative therapeutic effects of radioactive and chemical agents in neoplastic diseases of the hematopoietic system. *Am. J. Roentgenol.*, 58: 774, 1947.
4. Karnofsky, D. A. The bases for cancer chemotherapy. *Stanford M. Bull.*, 6: 257, 1948.
5. Karnofsky, D. A. Medical progress: chemotherapy of neoplastic disease. *New England J. Med.*, 239: 226, 260, 299, 1948.
6. Gellhorn, A. and Jones, L. O. Chemotherapy of malignant disease. *Am. J. Med.*, 6: 188, 1949.
7. Shimkin, M. B. and Bierman, H. R. Experimental chemotherapy of neoplastic diseases. *Radiology*, 53: 518, 1949.
8. Clark, R. L., Jr. The present status of cancer therapy. *Postgrad. Med.*, 6: 89, 1949.
9. Dodds, E. C. Chemotherapy in the treatment of malignant disease. *Brit. M. J.*, 2: 1191, 1949.
10. Cade, S. Chemotherapy in the treatment of malignant disease. *Brit. M. J.*, 2: 1193, 1949.
11. Paterson, R. The Treatment of Malignant Disease by Radium and X-rays. Baltimore, 1948. Williams & Wilkins Co.
12. Radiobiology; experimental and applied. *Brit. M. Bull.*, 4: 1, 1946.
13. Giese, A. C. Radiations and cell division. *Quart. Rev. Biol.*, 22: 253, 1947.
14. Spear, F. G. Editor: Supplement No. 1. Certain aspects of the action of radiation on living cells. *Brit. J. Radiol.*, 1947.
15. Lea, D. E. Actions of Radiations on Living Cells. New York, 1947. Macmillan Co.

16. Bloom, W. Editor: Histopathology of Irradiation from External and Internal Sources. New York, 1948. McGraw-Hill Book Co., Inc.
17. Dobson, R. L. and Lawrence, J. H. Physiological effects of radiant energy. *Ann. Rev. Physiol.*, 10: 479, 1948.
18. Zirkle, R. E. Relationships between chemical and biological effects of ionizing radiations. *Radiology*, 52: 846, 1949.
19. Warren, S. L. Effects of radiation on normal tissues. *Arch. Path.*, 34: 443, 1942; 35: 121, 1943.
20. Jacox, H. W. Editorial: Palliative roentgen therapy. *Radiology*, 53, 750, 1949.
21. Koller, P. C. and Smithers, D. W. Cytological analysis of the response of malignant tumors to irradiation as an approach to the biological basis for dosage in radiotherapy. *Brit. J. Radiol.*, 19: 89, 1946.
22. Karnofsky, D. A., Thiersch, J. B., Ridgway, L. P. and Patterson, P. A. (Unpublished data.)
23. Jacobson, L. O., Marks, E. K., Gaston, E. O., Simmons, E. L. and Block, M. H. Studies on radiosensitivity of cells. *Science*, 107: 248, 1948.
24. Ellinger, F. The problem of recovery from radiation effects. *Radiology*, 40: 62, 1943.
25. Glucksmann, A. Quantitative histological analysis of radiation effects in human carcinomata. *Brit. M. Bull.*, 4: 26, 1946.
26. Glucksmann, A. Relation of radiosensitivity and radiocurability to the histology of tumour tissue. *Brit. J. Radiol.*, 21: 559, 1948.
27. Graham, R. M. The effect of radiation on vaginal cells in cervical carcinoma. I. Description of cellular changes. II. The prognostic significance. *Surg., Gynec. & Obst.*, 84: 153, 166, 1947.
28. Graham, J. B. and Graham, R. M. Pharmacological modification of resistance to radiation—a preliminary report. *Proc. Nat. Acad. Sc.*, 35: 102, 1949.
29. Patt, H. M., Straube, R. L., Tyree, E. B., Swift, M. N. and Smith, D. E. Influence of estrogens on the acute x-irradiation syndrome. *Am. J. Physiol.*, 159: 269, 1949.
30. Ellinger, F. Some effects of desoxycorticosterone acetate on mice irradiated with x-rays. *Proc. Soc. Exper. Biol. & Med.*, 64: 31, 1947.
31. Patt, N. M., Tyree, E. B., Straube, R. L. and Smith, D. E. Cysteine protection against x-irradiation. *Science*, 110: 213, 1949.
32. Goldfeder, A., Cohen, L., Miller, C. and Singer, M. Agents influencing experimental radiation injury. Effects of folic acid and pyridoxine. *Proc. Soc. Exper. Biol. & Med.*, 67: 272, 1948.
33. Karnofsky, D. A., Burchenal, J. H., Ormsbee, R. A., Cornman, I. and Rhoads, C. P. Experimental observations on the use of the nitrogen mustards in the treatment of neoplastic diseases. In Approaches to tumor chemotherapy. Pp. 293. Am. A. Advance. Sc., 1947.
34. Mitchell, J. S. Clinical trials of tetra-sodium 2-methyl-1:4-naphthohydroquinone diphosphate, in conjunction with x-ray therapy. *Brit. J. Cancer*, 2: 351, 1948.
35. Mitchell, J. S.: Histological changes produced by large doses of tetrasodium 2-methyl-1:4-naphthohydroquinone diphosphate in some human tumors. *Experientia*, 5: 293, 1949.
36. Karnofsky, D. A., Burchenal, J. H. and Escher, G. C. Chemotherapy of neoplastic diseases. *M. Clin. North America* (in press).
37. Philips, F. Recent advances in the pharmacology of 2-haloethyl amines and sulfides. *Pharmacol. Rev.* (in press).
38. Karnofsky, D. A. The nitrogen mustards in the treatment of neoplastic disease. In: Advances in Internal Medicine. Interscience Pub., New York, 1950.
39. Burchenal, J. H., Lester, R. A., Riley, J. B. and Rhoads, C. P. Studies on the chemotherapy of leukemia. I. Effect of certain nitrogen mustards and carbamates on transmitted mouse leukemia. *Cancer*, 1: 393, 1948.
40. Shapiro, D. M., Goldin, A., Landing, B. H., Bergner, A. D., Faiman, F. and Goldberg, B. Cancer chemotherapy: analysis of results of different screening techniques with nitrogen mustard analogues. *Cancer*, 2: 100, 1949.
41. Burchenal, J. H. The newer nitrogen mustards in the treatment of leukemia. *Radiology*, 50: 494, 1948.
42. Graef, I., Karnofsky, D. A., Jager, V. B., Krichesky, B. and Smith, H. W. The clinical and pathologic effects of the nitrogen and sulfur mustards in laboratory animals. *Am. J. Path.*, 24: 1, 1948.
43. Auerbach, C., Robson, J. M. and Carr, J. G. The chemical production of mutations. *Science*, 105: 243, 1947.
44. Boyland, E. and Horning, E. S. The induction of tumours with nitrogen mustards. *Brit. J. Cancer*, 3: 118, 1949.
45. Bodenstein, D. The effects of nitrogen mustard on embryonic amphibian development. Part 1. Ectodermal effects. *J. Exper. Zool.*, 104: 311, 1947. Part 2. Effects on eye development. *J. Exper. Zool.*, 108: 93, 1948.
46. Jacobson, L. O., Marks, E. K., Gaston, E. and Block, M. H. The effects of nitrogen mustard on induced erythroblastic hyperplasia in rabbits. *J. Lab. & Clin. Med.*, 34: 902, 1949.
47. Bierman, H. R., Shimkin, M. B., Mettier, S. R., Weaver, J., Berry, W. C. and Wise, S. P., III. Methyl bis (beta-chloroethyl) amine in large doses in treatment of neoplastic diseases. *California Med.*, 71: 117, 1949.
48. Medinger, F. G. and Craver, L. F. Total body irradiation with review of cases. *Am. J. Roentgenol.*, 48: 651, 1942.
49. Jacobson, L. O., Spurr, C. L., Guzman Barron, E. S., Smith, T., Lushbaugh, C. and Dick, G. F. Nitrogen mustard therapy. Studies on the effect of methyl-bis (beta-chloroethyl) amine hydrochloride on neoplastic diseases and allied disorders of the hemopoietic system. *J. A. M. A.*, 132: 263, 1946.
50. Goodman, L. S., Wintrobe, M. M., Dameshek, W., Goodman, M. J., Gilman, A. and McLennan, M. T. Use of methyl-bis (beta-chloroethyl) amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain

allied and miscellaneous disorders. *J. A. M. A.*, 132: 126, 1946.

51. KARNOFSKY, D. A., CRAVER, L. F., RHOADS, C. P. and ABELS, J. C. An evaluation of methyl-bis (β-chloroethyl) amine hydrochloride and tris (β-chloroethyl) amine hydrochloride (nitrogen mustards) in the treatment of lymphomas, leukemia, and allied diseases. In Approaches to Tumor Chemotherapy. P. 319. *Am. A. Adv. Sc.*, 1947.
52. APTHOMAS, M. I. R. and CULLUMBINE, H. Nitrogen mustards in Hodgkin's disease: report on 21 cases and 4 of other reticuloses. *Lancet*, 1: 899, 1947.
53. WINTROBE, M. M., HUGULEY, C. M., JR., MCLENNAN, M. T. and DE CARVALHO LIMA, L. P. Nitrogen mustard as a therapeutic agent for Hodgkin's disease, lymphosarcoma and leukemia. *Ann. Int. Med.*, 27: 529, 1947.
54. WINTROBE, M. M., and HUGULEY, C. M., JR. Nitrogen mustard therapy for Hodgkin's disease, lymphosarcoma, the leukemias, and other disorders. *Cancer*, 1: 357, 1948.
55. DAMESHEK, W., WEISFUSE, L. and STEIN, T. Nitrogen mustard therapy in Hodgkin's disease. *Blood*, 4: 338, 1949.
56. ZANES, R. P., DOAN, C. A. and HOSTER, H. A. Studies in Hodgkin's syndrome. VII. Nitrogen mustard therapy. *J. Lab. & Clin. Med.*, 33: 1002, 1948.
57. CRAVER, L. F. The nitrogen mustards: clinical use. *Radiology*, 50: 486, 1948.
58. ERF, L. A. and BAUER, R. D. The clinical effect of nitrogen mustard on Hodgkin's disease. *Am. J. Clin. Path.*, 19: 372, 1949.
59. HENSTELL, H. H., TOBER, J. N. and NEWMAN, B. A. The influence of nitrogen mustard on mycosis fungoides. *Blood*, 2: 564, 1947.
60. OSBORNE, E. D., JORDON, J. W., HOAK, F. C. and PSCHIERER, F. J. Nitrogen mustard therapy in cutaneous blastomatous disease. *J. A. M. A.*, 135: 1123, 1947.
61. SKINNER, E. F., CARR, D. and DENMAN, W. E. The treatment of inoperable bronchogenic carcinoma with methyl-bis. *J. Thoracic Surg.*, 17: 428, 1948.
62. BOYLAND, E., CLEGG, J. W., KOLLER, P. C., RHODEN, E. and WARWICK, O. H. The effect of chloroethylamines on tumours, with special reference to bronchogenic carcinoma. *Brit. J. Cancer*, 2: 17, 1948.
63. KARNOFSKY, D. A., ABELMAN, W., CRAVER, L. F. and BURCHENAL, J. H. The use of nitrogen mustards in the palliative treatment of bronchogenic carcinoma. *Cancer*, 1: 634, 1948.
64. BURCHENAL, J. H., MYERS, W. P. L., CRAVER, L. F. and KARNOFSKY, D. A. The nitrogen mustards in the treatment of leukemia. *Cancer*, 2: 1, 1949.
65. PHILLIPS, R. F. and KARNOFSKY, D. A. (Personal communication.)
66. SKIPPER, H. W. Carbamates in the chemotherapy of leukemia. v. Observation of a possible antileukemic synergism between urethane and methyl-bis (β-chloroethyl) amine. *Cancer*, 2: 475, 1949.
67. DUSTIN, P. Cytological action of ethylcarbamate (urethane) and other carbamic esters in normal and leukaemic mice and in rabbits. *Brit. J. Cancer*, 1: 48, 1947.
68. CRUZ, W. O. and MOUSSATACHE, H. Acute thrombocytopenia induced in dogs by administration of urethane (ethyl carbamate). *Blood*, 3: 793, 1948.
69. NETTLESHIP, A. and HENSHAW, P. S. Induction of pulmonary tumors in mice with ethyl carbamate (urethane). *J. Nat. Cancer Inst.*, 4: 309, 1943.
70. JAFFE, W. G. Carcinogenic action of ethyl urethane on rats. *Cancer Research*, 7: 107, 1947.
71. HADDOW, A. and SEXTON, W. A. Influence of carbamic esters (urethanes) on experimental animal tumours. *Nature, London*, 157: 500, 1946.
72. LAW, L. W. Urethane (ethyl carbamate) therapy in spontaneous leukemias in mice. *Proc. Nat. Acad. Sc.*, 33: 204, 1947.
73. SKIPPER, H. E. and BRYAN, C. E. Carbamates in the chemotherapy of leukemia. III. The relationship between chemical structure and antileukemic action of a series of urethan derivatives. *J. Nat. Cancer Inst.*, 9: 391, 1949.
74. LARSEN, C. D. Evaluation of carcinogenicity of series of esters of carbamic acid. *J. Nat. Cancer Inst.*, 8: 99, 1947.
75. BRYAN, C. E., SKIPPER, H. W. and WHITE, L., JR. Carbamates in the chemotherapy of leucemia. IV. The distribution of radioactivity in tissues of mice following injection of carbonyl-labeled urethane. *J. Biol. Chem.*, 177: 941, 1949.
76. MITCHELL, J. H., HUTCHISON, O. S., SKIPPER, H. E. and BRYAN, C. E. Carbamates in the chemotherapy of leucemia. VII. The rate of catabolism of urethane in normal and neoplastic mice. *J. Biol. Chem.*, 180: 675, 1949.
77. WEBSTER, J. J. Urethane in leukemia. *J. A. M. A.*, 135: 901, 1947.
78. PATERSON, E., HADDOW, A., APTHOMAS, I. and WATKINSON, J. M. Leukemia treated with urethane compared with deep x-ray therapy. *Lancet*, 1: 677, 1946.
79. HIRSCHBOECK, J. S., LINDERT, M. C. F., CHASE, J. and CALVY, T. L. Effects of urethane in the treatment of leukemia and metastatic malignant tumors. *J. A. M. A.*, 136: 90, 1948.
80. BERMAN, L. and AXELROD, A. R. Effect of urethane on malignant disease: hematologic and histologic observations on patients with carcinoma, leukemia and related diseases. *Am. J. Clin. Path.*, 18: 104, 1948.
81. HUGGINS, C., YU, S. T. and JONES, R., JR. Inhibitory effects of ethyl carbamate on prostatic cancer. *Science*, 106: 147, 1947.
82. LAPIDES, J. Clinical value of urethane therapy in prostatic cancer. *Cancer*, 2: 469, 1949.
83. LOGE, J. P. and RUNDLES, R. W. Urethane (ethyl carbamate) therapy in multiple myeloma. *Blood*, 4: 201, 1949.
84. RUNDLES, R. W. and REEVES, R. J. Multiple myeloma. II. Variability of roentgen appearance and effect of urethane therapy on skeletal disease. *Am. J. Roentgenol.* (in press).
85. DILLON, E. S., DILLON, M. L. and RUNDLES, R. W. Changes in electrophoretic patterns of sera in patients with multiple myeloma treated with urethane. *Am. J. Med.*, 7: 242, 1949.

86. Snapper, I. Stilbamidine and pentamidine in multiple myeloma. *J. A. M. A.*, 133: 157, 1947.
87. Lawrence, J. H. Some tracer and therapeutic studies with artificial radioactivity. *Brit. J. Radiol.*, 21: 531, 1948.
88. Reinhard, E. H., Moore, C. V., Bierbaum, O. S. and Moore, S. Radioactive phosphorus as a therapeutic agent. A review of the literature and analysis of the results of treatment of 155 patients with various blood dyscrasias, lymphomas, and other malignant neoplastic diseases. *J. Lab. & Clin. Med.*, 31: 107, 1946.
89. Doan, C. A., Wiseman, B. K., Wright, C-S., Geyer, J. H., Myers, W. and Myers, J. W. Radioactive phosphorus, P^{32}: six year clinical evaluation of internal radiation therapy. *J. Lab. & Clin. Med.*, 32: 943, 1947.
90. Craver, L. F. Recent advances in treatment of lymphomas, leukemias and allied disorders. *Bull. New York Acad. Med.*, 24: 3, 1948.
91. Lawrence, J. H., Dobson, R. L., Low-Beer, B. V. A. and Brown, B. R. Chronic myelogenous leukemia; study of 129 cases in which treatment was with radioactive phosphorus. *J. A. M. A.*, 136: 672, 1948.
92. Lawrence, J. H., Low-Beer, B. V. A. and Carpender, J. W. J. Chronic lymphatic leukemia. A study of 100 patients treated with radioactive phosphorus. *J. A. M. A.*, 140: 585, 1949.
93. Lawrence, J. H. The control of polycythemia by bone marrow inhibition. A ten year study on 172 patients. *J. A. M. A.*, 141: 13, 1949.
94. Forkner, C. E. Leukemia and Allied Diseases. New York, 1938. Macmillan Co.
95. Burchenal, J. H., Bendich, A., Brown, G. B., Elion, G. B., Hitchings, G. H., Rhoads, C. P. and Stock, C. C. Preliminary studies on the effect of 2,6-diaminopurine on transplanted mouse leukemia. *Cancer*, 2: 119, 1949.
96. Kidder, G. W., Dewey, V. C. and Parks, R. E., Jr. Purine metabolism in Tetrahymena and its relation to malignant cells in mice. *Science*, 109: 511, 1941.
97. Armistead, G. C., Jr., Burchenal, J. H., Karnofsky, D. A. and Southam, C. M. Preliminary studies on the clinical toxicity of 5-amino-7-hydroxy-1-v-triazolo(d) pyrimidine (guanazolo). *Cancer* (in press).
98. Burchenal, J. H., Karnofsky, D. A., Southam, C. M., Myers, W. P. L., Craver, L. F., Dargeon, H. W. and Rhoads, C. P. The effects of 4-amino-pteroylglutamic acid and related compounds on neoplastic disease. (To be published.)
99 Gellhorn, A. and Jones, L. O. Pyridoxine deficient diet and desoxypyridoxine in the therapy of lymphosarcoma and acute leukemia in man. *Blood*, 4: 60, 1949.
100. Franklin, A. L., Stokstad, E. L. R. and Jukes, T. H. Observations on the effect of 4-amino-pteroylglutamic acid on mice. *Proc. Soc. Exper. Biol. & Med.*, 67: 398, 1948.
101. Thiersch, J. B. and Philips, F. S. Folic acid and antagonists in neoplastic disease. *Am. J. M. Sc.*, 217: 575, 1949.
102. Farber, S., Diamond, L. K., Mercer, R. D., Sylvester, R. F., Jr. and Wolff, J. A. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-amino-pteroylglutamic acid (Aminopterin). *New England J. Med.*, 238: 787, 1948.
103. Rhoads, C. P. Advances in treatment of malignant disease. *Bull. New York Acad. Sc.*, 25: 271, 1949.
104. Karnofsky, D. A., Patterson, P. A. and Ridgway, L. P. Effect of folic acid, "4-amino" folic acids and related substances on growth of chick embryo. *Proc. Soc. Exper. Biol. & Med.*, 71: 447, 1949.
105. Hertz, R. and Tullner, W. W. Quantitative interference with estrogen-induced tissue growth by folic acid antagonists. *Endocrinol.*, 44: 278, 1949.
106. Philips, F. S. and Thiersch, J. B. Studies on the actions of 4-amino pteroylglutamic acid in rats and mice. *J. Pharmacol. & Exper. Therap.*, 95: 303, 1949.
107. Burchenal, J. H., Burchenal, J. R., Kushida, M. N., Johnston, S. F. and Williams, B. S. Studies on the chemotherapy of leukemia. II. The effect of 4-amino-pteroylglutamic acid and 4-amino-N^{10}-methyl-pteroylglutamic acid on transplanted mouse leukemia. *Cancer*, 2: 113, 1949.
108. Schoenbach, E. B., Goldin, A., Goldberg, B. and Ortega, L. G. The effect of folic acid derivatives on sarcoma 180. *Cancer*, 2: 57, 1949.
109. Sugiura, K., Moore, A. E. and Stock, C. C. The effects of aminopterin on the growth of carcinoma, sarcoma and melanoma in animals. *Cancer*, 2: 491, 1949.
110. Stock, C. C., Biesele, J. J., Burchenal, J. H., Karnofsky, D. A., Moore, A. E. and Sugiura, K. Folic acid analogs and experimental tumors. *Bull. New York Acad. Sc.* (in press).
111. Burchenal, J. H., Kushida, M. N., Johnston, S. F. and Cremer, M. A. Prevention of chemotherapeutic effects of 4-amino-N^{10}-methyl-pteroylglutamic acid on mouse leukemia by pteroylglutamic acid. *Proc. Soc. Exper. Biol. & Med.*, 71: 559, 1949.
112. Karnofsky, D. A., Thiersch, J. B. and Ingle, D. J. Some observations on the mechanism of action of 4-aminopteroylglutamic acid (Aminopterin) in the rat. (To be published.)
113. Wolman, I. J., Eglick, P., Dickstein, B. and Githens, J. Leukemia in childhood. Preliminary report of response to Aminopterin. *Pennsylvania M. J.*, 52: 474, 1949.
114. Farber, S. Some observations on the effect of folic acid antagonists on acute leukemia and other forms of incurable cancer. *Blood*, 4: 160, 1949.
115. Dameshek, W. The use of folic acid antagonists in the treatment of acute and subacute leukemia. A preliminary statement. *Blood*, 4: 168, 1949.
116. Meyer, L. M., Fink, H., Sawitsky, A., Rowen, M. and Ritz, N. D. Aminopterin (a folic acid antagonist) in the treatment of leukemia. *Am. J. Clin. Path.*, 19: 119, 1949.
117. Burchenal, J. H., Robinson, E., Johnston, S. F. and Kushida, M. N. The induction of resistance to 4-amino-N^{10}-methyl-pteroylglutamic acid in a strain of transmitted mouse leukemia. *Science* (in press).

118. Berman, L., Axlerod, A. R., Vonderheide, E. C. and Sharp, E. A. Use of a folic acid antagonist in chronic leukemia. *Am. J. Clin. Path.*, 19: 127, 1949.
119. Seidlin, S. M., Marinelli, L. D. and Oshry, E. Radioactive iodine therapy; effect on functioning metastases of adenocarcinoma of thyroid. *J. A. M. A.*, 132: 838, 1946.
120. Marinelli, L. D., Foote, F. W., Hill, R. F. and Hocker, A. F. Retention of radioactive iodine in thyroid carcinomas: histopathologic and radio-autographic studies. *Am. J. Roentgenol.*, 58: 17, 1947.
121. Fitzgerald, P. J. and Foote, F. W., Jr. The function of various types of thyroid carcinoma as revealed by the radio-autographic demonstration of radioactive iodine (I^{131}). *J. Clin. Endocrinol.* 9: 1153, 1949.
122. Rawson, R. W., Marinelli, L. D., Skanse, B. N., Trunnell, J. and Fluharty, R. G. The effect of total thyroidectomy on the function of metastatic thyroid cancer. *J. Clin. Endocrinol.*, 8: 826, 1948.
123. Seidlin, S. M., Rossman, I., Oshry, E. and Siegel, E. Radioiodine therapy of metastases from carcinoma of the thyroid: a six-year progress report. *J. Clin. Endocrinol.*, 9: 1122, 1949.
124. Trunnell, J. B., Marinelli, L. D., Duffy, B. J., Jr., Hill, R., Peacock, W. and Rawson, R. W. The treatment of metastatic thyroid cancer with radioactive iodine: credits and debits. *J. Clin. Endocrinol.*, 9: 1138, 1949.
125. Herger, C. C. and Sauer, H. R. Consideration of effect of androgen control treatment of carcinoma of prostate. *New York State J. Med.*, 47: 494, 1947.
126. Nesbit, R. M. and Plumb, R. T. Prostatic carcinoma; follow-up on 795 patients treated prior to endocrine era and comparison of survival rates between these and patients treated by endocrine therapy. *Surgery*, 20: 263, 1946.
127. Deming, C. L. Hormonal treatment of prostatic malignancy. *Bull. New York Acad. Med.*, 22: 88, 1946.
128. Treves, N. Castration as a therapeutic measure in cancer of the male breast. *Cancer*, 2: 191, 1949.
129. Nathanson, I. T. Hormonal alteration of advanced cancer of breast. *S. Clin. North America*, 27: 1144, 1947.
130. Adair, F. E., Mellors, R. C., Farrow, J. H., Woodard, H. Q., Escher, G. C. and Urban, J. A. The use of estrogens and androgens in advanced mammary cancer: clinical and laboratory study of one hundred and five female patients. *J. A. M. A.*, 140: 1193, 1949.
131. Therapeutic Trials Committee, Council on Pharmacy and Chemistry, A. M. A.: Proceedings of the First Conference on Steroid Hormones and Mammary Cancer. Pp. 1–205, 1949.
132. American Medical Association, Council on Pharmacy and Therapy. Estrogens and androgens in mammary cancer: a progress report. *J. A. M. A.*, 140: 1214, 1949.
133. MacDonald, E. J. The present incidence and survival picture in cancer and the promise of improved prognosis. *Bull. Am. Coll. Surgeons*, 33: 75, 1948.
134. Craver, L. F. Irradiation in the lymphomatoid diseases. *Bull. New York Acad. Med.*, 15: 442, 1939.
135. Craver, L. F. Lymphomas and leukemia. *Bull. New York Acad. Med.*, 23: 79, 1947.
136. Krebs, C. and Bichel, J. Results of roentgen treatment of chronic myelogenous leucosis. *Acta radiol.*, 28: 697, 1947.
137. Hart, P. L. deV. A case of monocytic leukemia treated with Aminopterin. *Brit. M. J.*, 2: 363, 1949.
138. Roswit, B. and Kaplan, G. The role of nitrogen mustard (HN2) as a systemic adjunct to the radiation therapy of certain malignant diseases. *Am. J. Roentgenol.*, 61: 626, 1949.
139. Kurnick, N. B., Paley, K. R., Fieber, M. H. and Adler, D. K. Treatment of malignant disease with nitrogen mustard. *Ann. Int. Med.*, 30: 974, 1949.
140. Shullenberger, C. C., Watkins, C. H. and Kierland, R. R. Experiences with nitrogen mustard therapy. *J. A. M. A.*, 139: 773, 1949.
141. Goldman, R., Egeberg, R. O., Ware, E. R. Evans, E. R. and Fishkin, B. G. Clinical experience with nitrogen mustard therapy. *Arch. Int. Med.*, 82: 125, 1948.
142. Kennedy, B. J. and Aub, J. C. The Therapeutic Indications for Nitrogen Mustards in Lymphomas. *M. Clin. North America*, Mass. General Hosp. Number, p. 1301. Philadelphia, 1949. W. B. Saunders & Co.
143. Spitz, S. The histological effects of nitrogen mustards on human tumors and tissues. *Cancer*, 1: 383, 1948.
144. Garland, L. H. and Kennedy, B. R. Roentgen treatment of multiple myeloma. *Radiology*, 50: 297, 1948.
145. Hall, B. E. and Watkins, C. E. Medical use of radioactive isotopes. 1. Radioactive isotopes in hematologic disturbances and neoplasms. *Am. J. M. Sc.*, 213: 621, 1947.
146. Faloon, W. W. and Gorham, L. W. Clinical experience with nitrogen mustard. *New York State J. Med.*, 48: 612, 1948.
147. Dargeon, H. W. Cancer in children from birth to fourteen years of age. *J. A. M. A.*, 136: 459, 1948.
148. Dargeon, H. W. Chemotherapy in a case of eosinophilic granuloma. *Pediatrics* (in press).
149. Dobriner, K. The excretion of steroids in health and in disease. *Acta de L'Union Internat. Contre le Cancer*, 6: 315, 1949.
150. Dobriner, K., Lieberman, S. and Rhoads, C. P. Studies in steroid metabolism. I. Methods for the isolation and quantitative estimation of neutral steroids present in human urine. *J. Biol. Chem.*, 172: 241, 1948.
151. Lieberman, S., Dobriner, K., Hill, B. R., Fleser, L. F. and Rhoads, C. P. Studies in steroid metabolism. II. Identification and characterization of ketosteroids isolated from the urines of healthy and diseased persons. *J. Biol. Chem.*, 172: 263, 1948.
152. Rhoads, C. P. Clinical endocrinology and the cancer problem. *J. Urol.*, 60: 797, 1948.

153. PEARSON, O. H., ELIEL, L. P., RAWSON, R. W., DOBRINER, K. and RHOADS, C. P. ACTH and cortisone-induced regression of lymphoid tumors. *Cancer*, 2: 943, 1949.

154. HAHN, P. F. and SHEPPARD, C. W. Therapeutic use of radioactive elements in malignancy. *Ann. Int. Med.*, 28: 598, 1948.

155. DOUGHERTY, E. C. and LAWRENCE, J. H. Heavy and Radioactive Isotopes in Clinical and Experimental Medicine. In: Advances in Biological and Medical Physics, edited by LAWRENCE, J. H. and HAMILTON, J. G. New York, 1948. Academic Press.

156. BLOCK, M. H., JACOBSON, L. O., NEAL, W. B., JR. and SMITH, T. R. The use of radioarsenic (As^{76}) in the treatment of leucemia and allied disorders of the hematopoietic tissues. *J. Lab. & Clin. Med.*, 33: 1649, 1948.

157. EVANS, T. C., LENZ, M., DONLAN, C. P. and LE MAY, M. J. Effects of radioactive sodium on leukemia and allied diseases, preliminary report. *Am. J. Roentgenol.*, 59: 469, 1948.

158. DUDLEY, H. C. and MADDOX, G. E. Deposition of radio gallium (Ga^{72}) in skeletal tissues. *J. Pharmacol. & Exper. Therap.*, 96: 224, 1949.

159. TURNER, J. C. and MULLIKEN, B. Parasitization of mouse sarcoma 180 by vaccine virus and its effect on tumor growth. *Cancer Research*, 7: 774, 1947.

160. MOORE, A. E. The destructive effect of the virus of Russian Far East encephalitis on the transplantable mouse sarcoma 180. *Cancer*, 2: 525, 1949.

161. HOSTER, H. A., ZANES, R. P., JR. and VON HAMM, E. Studies in Hodgkin's syndrome. IX. The association of "viral" hepatitis and Hodgkin's disease. (A preliminary report.) *Cancer Research*, 9: 473, 1949.

162. BOYLAND, E. Chemistry of neoplastic tissue. *Ann. Rev. Biochem.*, 18: 217, 1949.

Clinic on Psychosomatic Problems

Ulcerative Colitis

THESE cases are chosen to illustrate the relation between psychiatric and medical factors in the production of symptoms. They are part of the Harvard teaching on the Psychiatric and Children's Medical Services of the Massachusetts General Hospital. These psychiatric conferences are edited by Drs. Stanley Cobb and Henry H. W. Miles. Publication is made possible by a grant from the Josiah Macy, Jr., Foundation.

A TWENTY-SEVEN year old man (No. 431182) was transferred to the Massachusetts General Hospital because of bloody diarrhea, weakness and weight loss which had begun nine weeks previously and had gradually become worse despite treatment in another hospital. The patient was an army officer who had been stationed for some months in the South. Upon transfer to a post near Boston he had spent a week of strenuous social activity involving late hours and a good deal of drinking. It was at this time, while suffering from an upper respiratory infection, that he noted abdominal cramps and tenesmus and began having six or seven loose stools daily. The diarrhea became worse and he was hospitalized; despite low-residue diet, paregoric, antispasmodics, supplementary vitamins and oral sulfonamides, his condition failed to improve. He had as many as twenty stools daily, abdominal cramps, nausea and vomiting and a spiking temperature to about 101°F. each afternoon.

Past medical history was non-contributory except for an episode of colitis which had occurred four years before the present illness. The patient had been taking final examinations in graduate school when he developed painless diarrhea. Because of streaks of blood in the stools he had sought medical advice and had been hospitalized. Proctoscopy had revealed diffuse reddening of the mucosa but no gross ulceration. Barium enema had shown findings consistent with early ulcerative colitis. Treatment by low-residue, bland diet and bed rest brought about a cessation of symptoms within three weeks. No further bowel disturbances had occurred until the present attack.

Physical examination revealed a gaunt, dehydrated, apathetic young man with evidence of considerable weight loss. The abdomen was diffusely tender without palpable organs or masses.

The laboratory data were consistent with the illness. There were leukocytosis, increased sedimentation rate, moderate anemia, slightly elevated non-protein nitrogen and low serum proteins. The stools contained varying amounts of gross blood and repeated microscopic examinations were negative for parasites, cysts or ova. Proctoscopy revealed a granular mucosa with punctate hemorrhages and extensive ulceration. Barium enema showed absence of haustral markings, and the outline of the colon from the sigmoid to the cecum was rough and irregular.

The patient was quite depressed, withdrawn and apathetic. It was suspected that his attitude reflected serious emotional problems; and because he remained so uncommunicative and discouraged, it was decided to enlist the aid of a psychiatrist. About forty interviews were carried out in a three-month period during which the patient was under constant medical supervision, receiving parenteral fluids, electrolytes, vitamins and transfusions. The clinical course was that of a severe case of ulcerative colitis. At times the patient seemed to be improving slowly, only to have an increase in the diarrhea and loss of weight. The patient was presented at a staff conference of the Psychiatric Service after fourteen weeks of hospitalization.

The patient was pale and hollow-cheeked, lying quietly in bed and showing little interest in the group of doctors. He answered questions briefly and apathetically, giving the impression that he was tired and slightly depressed.

DISCUSSION

DR. ERICH LINDEMANN: I will give a brief summary of the family situation and social history first. The parents are Jewish immigrants, the father having formerly managed a small clothing store. The family as a whole has a strong sense of "social climbing." An older brother became a lawyer and the patient tried to follow his example; although he achieved a postgraduate degree, he was disappointed in his failure to be as "successful" as his brother. The father had what was probably a psychotic episode when the patient was three years old and is now a reticent, stubborn man who shares practically no emotional experiences with the rest of the family. As a result of his personality change his only employment in recent years has been as a day laborer. The mother has been the important figure in keeping the family together and supporting it. There has always been tension and mutual accusation between the parents and a clash between old-fashioned Jewish customs and the so-called modern ways.

The patient was breast-fed for six months, then abruptly weaned by the mother who put bitter material on her nipples to facilitate the process. As a child the patient had no definite neurotic traits other than food finnickiness but he had no friends, tended to be seclusive and spent much time at home. His social adjustment was always poor and one might summarize his personality as one of shyness, retirement, lack of friends and a poverty of socially useful behavior.

As far as the interview material is concerned, I do not know very much about him because I could not use the probing type of inquiry we use on other patients. It has been necessary to avoid topics which might precipitate severe emotional disturbances since these might, in turn, bring about a dangerous exacerbation of the bowel condition. At first I saw him only ten minutes at a time, and for the first month I was flatly rejected.

Gradually we were able to talk more freely. We discussed things which he had not previously recognized as real difficulties —which is characteristic for him. He said he could not work, that he had ruined his status in his job and that there were certain clients whom he felt he wished to kill. Everything appeared to be gloomy and he wanted to be mean to people. There were only two situations in which he could feel really comfortable, namely, one, when he was at home with his mother, and two, when talking about baseball or casual matters "with the fellows."

In the ward the patient had become quite attached to the medical house officer saying it was because the latter was from Cuba and was different from the rest of us. He was quite upset when the house officer left the service and for a few weeks lost ground medically. Toward the end of that month (the second month of hospitalization) he was not doing well at all and I began to see that he felt uncomfortable with me. I pointed out to him that perhaps if we could be a little more outspoken with each other things would be better.

Finally about a month later he said that his real trouble was the racial problem. He had grown up with the idea that the whole world regarded Jews as conspicuous. He had found out that Gentile girls turned away when they discovered a boy was Jewish. He went out with many girls, always being rejected.

The patient then told of having had an attack of colitis during his freshman year at college, an episode which he had not previously admitted. At that time his mother was making sacrifices to send him money so that he could remain in college. He had tried to work his way through but had found it too difficult. He had attributed his diarrhea to the "bad food" which was served, left college and came home to his mother. He then attended a local uni-

versity so he could live at home and eat good food.

During the third month of his hospitalization here he became very much attracted to a female patient who visited the ward frequently and sat on his bed to talk. Then one day he told me that she had discovered he was Jewish, at least he had told her so, and her reaction was one of incredulity. She stopped coming to see him and he felt completely deflated. He made excuses saying that perhaps she was preoccupied with her own life or maybe her doctor had told her not to come see him any more.

We now shared an actual problem which we could work on together from day to day. I told him that we had to do something so he could accept the fact that he was Jewish, could be happy as such and could find a Jewish girl. He said he could not love girls. He had had dates with girls, had intercourse with them and then dropped them. He felt that his work was not his chief interest but by means of it he could be successful and could make his mother happy. Perhaps he might even afford to send her on a luxury trip some day. He was extremely devoted to his mother and wanted only to help her.

At this time I spoke to his mother who said that she could see an improvement in his spirits and attitude. She said he had always been quiet, and her only companion. I asked if the anti-Semitic situation had anything to do with his condition. She replied that he is an American and America has no such problems and that he needed to find the right girl. She is still possessive of him; she watches him from day to day. She asks, "When can I take him home where I can have the right diet for him?"

I think we have gradually begun to understand the boy's predicament. He has developed a morbid relationship with his mother and has had no opportunity to develop adequate relationships with his father or with other youngsters. He now finds himself a completely isolated individual. His mother is really standing in his way because he wants a different social and racial standard.

DR. JACOB E. FINESINGER: In his general attitude he is certainly not outgoing; yet he seems somewhat less resentful and I think he is reaching out a little. I gather there has been improvement in the bowel situation?

DR. JAMES G. MILLER: The bowel movements are somewhat less. Recent x-rays showed slight improvement.

DR. FREDERICK WYATT: He is more intelligent than the average individual. The Rorschach test suggests that he is unimaginative but aware of emotional turmoil with a high degree of tension. He cannot accept his emotions and tries to intellectualize them. He has great difficulty in making contact, is isolated and does not know what to do with his affects. There is evidence of marked immaturity and concern with the body.

The thematic apperception test indicates a succorant type (leaning toward others for dependency). "Somebody else will solve my problems." There are also indications of economic worries, social status worry, difficulties of interpersonal adjustments and a problem in the acceptance of the male role.

DR. FINESINGER: His hostility comes into his general behavior. His experience on the ward duplicates his past experiences with girls. He was glad to leave the South and get back home. The question in my mind is: What does this have to do with the colitis? Is there anything that correlates with the onset and clinical course of the disease?

DR. LINDEMANN: The transition from an impulse to its execution is blocked in this patient who has such poverty of expression. There is the danger for him that he might act out his impulses. If he were aroused emotionally, he might display very primitive behavior. His isolation and lack of technics of dealing with his impulses are the most important features. The bowel is a susceptible organ and reacts. I have traced this in other patients having bowel movements instead of a free expression of their impulses.

DR. HELENE DEUTSCH: I am very much interested in Dr. Lindemann's description of the patient's personality. We see so clearly

his ambivalence and his solution of it, so much determined by a protest against the mother. I have the same question that Dr. Finesinger asked and I am not satisfied with Dr. Lindemann's answer. The patient's isolation came as a result of impulses from which he could protect himself only by a lack of emotions. We see this in atypical obsessional neuroses. We also see it in cases of depersonalization without colitis.

We are looking for bridges between the personality and the organic symptom; I do not see the bridge in this case. There must be dreams, fantasies, other material. I am in complete agreement with the psychologic picture as presented but I am not satisfied with the interpretation of the colitis.

DR. FINESINGER: That is one of the major questions: Are his personality problems specifically related to the ulcerative colitis? Dr. Lindemann's technic was planned for supportive therapy; because of the danger of aggravating the colitis, it was not possible to use an exploratory type of therapy.

FURTHER TREATMENT

Another month of hospitalization resulted in little if any improvement in the condition of the bowel. Throughout the psychiatric interviews the patient was unable to accept the therapist as a model, so that the tendency to identify with the psychiatrist and copy his patterns of behavior did not occur. (This type of identification had proven helpful in the treatment of other persons with ulcerative colitis.) It finally became evident that an ileostomy would be necessary. He was finally persuaded to accept the operation and underwent surgery without excessive anxiety or depression. After a lengthy convalescence he was discharged in good physical condition with an adequately functioning ileostomy. He declined to return for further psychotherapy.

Postoperatively the patient improved slowly but steadily. His weight rose to normal and he was able to return to his job although for a few months he worked only two days a week because of persistent fatigue. He also complained during this time of insomnia and depression.

Three and a half years after the ileostomy he was interviewed by a psychiatrist and social worker for a detailed evaluation of his adjustment. He reported that he felt "perfectly well" except for occasional vague tension. He added that he still "held his emotions in check" as he had always done. There had been no fundamental changes in his personality. He still lived with his parents although he had married a nice Jewish girl and had a small son. He rationalized his reluctance to establish a home of his own by remarking on the difficulties of finding an apartment. There was definite improvement in his social relationships. He reported that marital relations were satisfactory although he and his wife did have some arguments because they were "temperamentally similar" and sometimes irritated each other.

Acceptance of the ileostomy had been cheerful and realistic. It was the opinion of the examiners that his personality problems were much less disturbing to him than they had been previously. It was believed that the psychotherapy had definitely contributed to a happier and more comfortable emotional life.

Five years after the ileostomy the patient underwent an elective procedure, total colectomy, from which he recuperated rapidly and without complications. At this time he had continued to adjust satisfactorily and had no symptoms or complaints.

COMMENT

This case presentation has been oriented toward the psychiatrist's role in the treatment of a severe psychosomatic disorder. The diagnosis of ulcerative colitis presented no difficulty; the clinical picture, proctoscopic and x-ray findings were typical. Because of the serious nature of the disease with secondary infection, electrolyte and vitamin depletion, loss of protein, etc., the patient was quite properly under the immediate jurisdiction of the Medical Service.

Psychiatric interviews were carried out in the medical ward, the psychiatrist first seeking to establish a good relationship with the patient. This required a long time and was helped by the psychiatrist's friendly approach and permissive attitude. Gradually the patient's major conflicts and personality problems became clear although it could not be demonstrated that they were specifically correlated with the onset of the illness.

The question of psychogenic factors in the etiology of ulcerative colitis has long been a matter for speculation.[1,2,3,4] A number of reports have indicated that persons suffering from this disease are apt to have many psychologic difficulties and often deal with their conflicts by inadequate or infantile means. No clearcut "personality profile" has emerged, and whether emotional traumas are etiologically related to the lesions in the bowel is not known. However, in those cases studied psychiatrically the onset of colitis is frequently related temporally to emotional stress.

Lindemann[5,6] and his associates at the Massachusetts General Hospital have had wide experience in recent years in the psychologic study and treatment of patients with ulcerative colitis. They have found that many of these persons have primitive types of fantasy, often violently aggressive, for which they have no adequate means of expression. Their relationship to the therapist may become infantile and excessively dependent as though the latter were not only omnipotent but also omniscient as well. This aspect of the transference situation differs from that of the typical patient with a character disorder or psychoneurosis. It is the insatiable dependency which often makes psychotherapy very difficult since one inevitably frustrates some of the patient's demands thus arousing strong hostile and aggressive feelings.

In most instances patients with ulcerative colitis have been unable to form adequate interpersonal relationships and have been deeply attached to one or two key figures in the social constellation. A severe emotional deprivation such as the loss through death or separation of the person to whom they are deeply attached often precedes the first attack of diarrhea by a few days or weeks.

In the case reported herein, the initial episode of colitis (which the patient mentioned only after three months of psychotherapy) occurred during his freshman year of college when he was away from home and mother for the first time. The significance of this fact is not known since it was not possible to use an explorative type of psychotherapy. It should be emphasized again as a matter of caution that the stirring up of emotional conflicts by injudicious zeal on the part of the psychiatrist may be followed by severe or even fatal aggravation of the lesions in the bowel.

In the present case there was a chronic progressive disease with irreversible lesions in the colon; one could not hope to influence the state of the bowel by psychotherapy. However, after proper surgical management had put the colon at physiologic rest, there was an opportunity to evaluate the patient's personal adjustment. In terms of social relationships, sexual adjustment and job satisfaction he had maintained definite improvement for five years. The close cooperation of internists, psychiatrist and surgeon was an important factor in giving the patient the best possible chance of achieving an adequate physical and psychologic adjustment.

[1] MURRAY, C. D. Psychogenic factors in the etiology of ulcerative colitis and bloody diarrhea. *Am. J. M. Sc.*, 180: 239, 1930.

[2] SULLIVAN, A. J. Psychogenic factors in ulcerative colitis. *Am. J. Dig. Dis.*, 2: 65, 1935.

[3] WITTKOWER, E. Ulcerative colitis: personality studies. *Brit. M. J.*, 2: 1356, 1938.

[4] GROEN, J. Psychogenesis and psychotherapy of ulcerative colitis. *Psychosom. Med.*, 9: 151, 1947.

[5] LINDEMANN, E. Psychiatric problems in conservative treatment of ulcerative colitis. *Arch. Neurol. & Psychiat.*, 53: 322, 1945.

[6] LINDEMANN, E. Unpublished data.

Clinico-pathologic Conference

Penicillin-resistant Subacute Bacterial Endocarditis*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, L. W., (No. 177833) was a white, married coal miner, sixty years of age, who entered the Barnes Hospital on November 6, 1949, complaining of chills, fever and general malaise. The family history revealed that the patient's father had died at an advanced age from a "stroke." Two sisters had died of cancer. The past history was of interest in that the patient had migratory joint pains at the age fifteen from which he apparently recovered completely. When he was twenty-eight, he contracted both syphilis and gonorrhea; he received between ten and twenty injections of salvarsan and in later years three separate serologic tests were said to have been negative. When he was 48 and again when he was fifty-four, he had episodes of renal colic; six months prior to his admission to the hospital he had a third attack. Ten months before entry the patient contracted an infection of his left eye, the etiologic nature of which was not clear. He was treated with penicillin and a sulfonamide with complete recovery.

Apart from the episodes noted the patient had enjoyed good general health until the age of forty-six at which time he suddenly coughed up a small amount of bright red blood on several occasions. Soon thereafter he developed attacks of palpitation and dyspnea and was treated for "heart trouble." His dyspnea improved but he was unable to return to work because of palpitation brought forth by exertion. Six months before he entered the hospital several of the patient's teeth were extracted because of advanced decay. Shortly thereafter the third attack of renal colic, noted in the past history, occurred and the patient was subjected to cystoscopy. On the day following cystoscopy he suddenly developed sharp, excruciating pain in the right heel which radiated up his right leg. He was sent to a hospital in the community in which he lived and remained there for twenty days during which period the pain in his leg gradually subsided. Four months before admission to the Barnes Hospital he had the first of a long series of shaking chills followed by fever which at times rose to 103.5°F. These episodes were associated with profound malaise, myalgia and arthralgia. Soon thereafter the left side of the patient's mouth became numb and drooped, and he had difficulty in speaking. No other evidence of muscular weakness appeared, however. Two months before admission he developed severe pain in the left leg, and soon thereafter a large purple spot appeared on the left foot. Chills, fever and malaise persisted and he was seen by a physician who gave him five injections of penicillin. Following this treatment there was moderate remission of the fever. During the six weeks preceding his admission to the Barnes Hospital the patient took a liquid medicine which was said to have contained penicillin; he also was thought to have had a short course of

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

aureomycin during which some improvement occurred. During the course of his illness he lost 33 pounds.

At the time of admission the patient's temperature was 39°C., pulse 100, respirations 24 and blood pressure 165/60. He appeared acutely ill and any movement apparently produced considerable generalized muscle pain. The skin was hot and dry but no petechiae were evident. The pupils reacted normally to light and accommodation and the eyegrounds were within normal limits. Pyorrhea was marked. The pharynx was injected and there was one small, bright red spot in the right buccal mucous membrane, possibly a petechia. The neck veins were not distended. The chest was emphysematous and a few crackling rales were heard at the left lung base. The left border of cardiac dullness was 10 cm. from the midsternal line in the fifth left interspace. The rhythm was regular. A questionable diastolic thrill was felt at the apex. At the base a grade II systolic murmur and an early, high-pitched, blowing diastolic murmur were heard. The diastolic murmur was transmitted down the left side of the sternum. At the apex a rumbling mid-diastolic murmur was thought to be present but at the time of admission the patient's heart rate was too rapid for accurate auscultation. The abdomen was held rigidly and no organs or masses were felt. Rectal examination was not remarkable. The left foot was cooler than the right and no arterial pulses could be felt on the left side; they were present on the right. No edema was present. The neurologic examination was within normal limits.

Laboratory data: Blood count: red cells, 4,820,000; hemoglobin, 11 gm.; white cells, 25,800; differential count: juvenile forms, 6 per cent; stab forms, 51 per cent; segmented forms, 36 per cent; lymphocytes, 6 per cent; monocytes, 1 per cent. Urinalysis: albumin, 1+; sugar, negative; microscopic, many granular casts and many red blood cell casts. Urine culture: negative. Stool: guaiac negative. Blood Kahn test: doubtful. Cardiolipin test: positive, undiluted. Kolmer-Wassermann test: negative. Blood chemistry: non-protein nitrogen, 36 mg. per cent; sugar, 90 mg. per cent; total protein, 7 gm. per cent; albumin, 3.6 gm. per cent; globulin, 3.4 gm. per cent; CO_2 combining power, 23.3 mEq./L.; chlorides, 94 mEq./L. Circulation time (decholin): 13 seconds. Venous pressure: 110 mm. of water. Blood culture: nonhemolytic streptococcus (Streptococcus liquefaciens); sensitivity tests (see Table 1). Throat culture: no predominant organism. Roentgenogram of the chest: "The cardiac silhouette is not unusual. There is pulmonary infiltration in the left lower lobe. Both leaves of the diaphragm are somewhat flat although the left side is elevated. An open film of the abdomen reveals a questionable right ureteral calculus and right nephrolithiasis." Electrocardiogram: sinus tachycardia.

TABLE 1
SENSITIVITY OF STREPTOCOCCUS LIQUEFACIENS RECOVERED FROM BLOOD CULTURES TO VARIOUS ANTIBIOTICS

Antibiotic	Amount	Results
Penicillin (in units)	5	+
	10	+
	20	±
Aureomycin (in micrograms)	0.5	±
	1.0	0
Chloromycetin (in micrograms)	4.0	±
	5.0	± to 0
Streptomycin (in micrograms)	20.0	±
	30.0	±
	50.0	0

+ = Growth
0 = No growth
± = Partial inhibition

As soon as the sensitivity of the organism recovered from the patient's blood was determined, he was begun on 4 gm. of aureomycin* per day orally in divided

* Supplied through the courtesy of Dr. James Ruegsegger of Lederle Laboratories.

doses. Soon after beginning this regimen his temperature became normal; thereafter it never rose above 37.6°C. throughout the remainder of his hospital course. Despite the fall in temperature, however, the first seven blood cultures taken after institution of aureomycin therapy were positive. After one week of aureomycin therapy the patient developed severe anorexia, nausea and vomiting; the dose of oral aureomycin was decreased. The patient was given 200 mg. of the drug intravenously twice a day. Blood cultures taken on the ninth, tenth and eleventh days after the institution of aureomycin therapy revealed growth in broth cultures only after ten days; pour plates remained sterile. All blood cultures thereafter were negative. The patient's gastrointestinal symptoms persisted and oral aureomycin was discontinued completely. He was given a total of 1.5 gm. of the antibiotic intravenously daily. His appetite did not return.

Two weeks after admission a chest film revealed partial atelectasis of the left lower lobe with a pleural effusion on the same side. The non-protein nitrogen had risen to 50 mg. per cent. The urine was repeatedly examined and many red blood cells and red blood cell casts were found. The red count had fallen to 3,400,000 and the hemoglobin to 7.5 gm. The total protein dropped to 5 gm. per cent. The apical diastolic murmur was easily audible after the patient's heart rate slowed.

Edema of the lower extremities as well as of the peri-orbital areas appeared. The patient was given two blood transfusions; following the second transfusion he became jaundiced. Neither the liver nor spleen was palpable but liver function tests were as follows: cephalin-cholesterol flocculation test 3+; thymol turbidity test, 14.6 units; icterus index, 32 units; total bilirubin, 11.6 mg. per cent; bilirubinglobin, 4.52 mg. per cent; sodium bilirubinate, 7.08 mg. per cent. During the first three days following the onset of jaundice neither urobilinogen nor urobilin were found in the urine. The stool contained bilirubin but no urobilinogen.

The patient developed troublesome hiccoughs which lasted several days. His jaundice persisted and the non-protein nitrogen rose further to 71 mg. per cent; anorexia continued. The daily dose of aureomycin was decreased to 1 gm.; and when the blood level was found to be 160 gamma per cc., the daily dose was reduced to 200 mg. intravenously. Subsequently, intravenous administration was stopped and 3 gm. were given daily by the oral route; later the dose was reduced to 2 gm. daily. The patient's jaundice gradually decreased and liver function tests also indicated improvement; the patient's anemia was greatly improved by the transfusions and his total protein rose to 6 gm. per cent. The edema diminished. The non-protein nitrogen, however, continued to rise, reaching a level of 125 mg. per cent although the patient's urinary output was satisfactory. The chlorides rose to 125 mEq./L. On the morning of December 25, 1949, the patient was found to be extremely weak and nauseated. An electrocardiogram was taken and showed isoelectric T waves in leads I and II and premature ventricular contraction. Many previous electrocardiograms had been unchanged from that recorded on admission. The patient failed rapidly and expired quietly.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: It is perfectly clear that this patient was suffering from bacterial endocarditis, and it will be of interest to discuss first the nature of the heart lesion on which the infection was engrafted. At the age of fifteen, this patient had migratory joint pains with presumable recovery. When he was twenty-eight, he had syphilis and when he entered the hospital at the age of sixty-four he had aortic insufficiency. Certainly rheumatic heart disease and syphilitic heart disease must both be considered as etiologic possibilities in view of aortic insufficiency. Dr. Taussig, do you think there is much likeli-

hood that this man had syphilitic heart disease?

DR. BARRETT L. TAUSSIG: Syphilitic heart disease is not a likely diagnosis here. It would be unusual for a patient to receive antisyphilitic therapy following the original infection, to have three negative serologic tests in the intervening years, and then to enter the hospital with syphilitic aortic insufficiency. Further, it seems probable that this man had mitral stenosis; and although a mitral diastolic murmur, the so-called Austin-Flint murmur, may be heard in aortic insufficiency due to syphilis, I think statistically it is much more likely that this patient had mitral and aortic valvular disease on the basis of rheumatic fever.

DR. THOMAS H. HUNTER: Another bit of evidence which supports Dr. Taussig's point of view is that bacterial endocarditis is an extremely rare complication of syphilitic valvular disease. Actually in syphilitic aortic insufficiency the valves themselves are not really involved but rather the ring of the aortic valve. I have seen only one case in which a syphilitic basis for bacterial endocarditis was proved.

DR. EDWARD MASSIE: I have seen three cases of bacterial endocarditis in the past three years in which I believe pathologic evidence of syphilis as the underlying lesion was clear-cut. I am sure, however, that my experience is not typical.

DR. ALEXANDER: Dr. Smith, you have been interested in this particular point. Would you care to comment?

DR. JOHN R. SMITH: There are series of cases in the literature in which the incidence of bacterial endocarditis in syphilitic aortic insufficiency is said to be as high as 3 per cent. However, such reports are in the minority.

DR. ALEXANDER: I think that Dr. Henry Christian once reported a series of 150 patients with bacterial endocarditis; in only one was syphilitic valvular disease the underlying lesion. Dr. Harford, would you tell us a little about the organism which was responsible for this man's infection.

DR. CARL G. HARFORD: The streptococcus isolated from this man's blood cultures, the so-called Streptococcus liquefaciens, belongs to the enterococci, a group which is, in general, more resistant to penicillin than are other non-hemolytic streptococci. The descriptive term, liquefaciens, is given to this organism because of its property of liquefying gelatin. That particular property is rare in streptococci, and the test therefore is of value in the laboratory when one attempts to differentiate this organism from others. The enterococci characteristically inhabit the gastrointestinal tract, but certainly may also be found in the mouth and one cannot say for certain what the portal of entry was in this instance. Subacute bacterial endocarditis often follows tooth extraction but it may follow other manipulative procedures as well. This man had a cystoscopy, for example, and it is conceivable that his infection was a result of transient bacteremia which followed that procedure.

DR. ALEXANDER: What is the incidence of subacute bacterial endocarditis with this particular enterococcus?

DR. HARFORD: It is very low.

DR. HUNTER: I would agree that Streptococcus liquefaciens is a fairly rare cause of bacterial endocarditis although the enterococci, as a whole, are responsible for perhaps 10 per cent of all cases.

DR. ALEXANDER: In the history we are told that the patient had a tooth extraction six months before entry. He was well, however, until three weeks later when cystoscopy was performed following his attack of renal colic. Immediately thereafter he developed the pain in his right leg and chills and fever. The pain was apparently extremely severe for the patient required hospitalization; it seems possible that the patient had an arterial occlusion at that time.

DR. W. BARRY WOOD, JR.: Has anyone ever studied the transient bacteremia which follows cystoscopy?

DR. ROBERT J. GLASER: There are a number of studies in the literature reporting

transient bacteremia after cystoscopy and other manipulations involving the genitourinary tract, particularly catheterization; so-called catheter fever is seen not uncommonly and is said to be due to transient bacteremia following that procedure. Often the organism recovered from the blood following instrumentation of the genitourinary tract is a gram-negative rod but it may be an enterococcus.

DR. ALEXANDER: Dr. Hunter, would you comment on the sensitivity to the various antibiotics which this organism exhibited?

DR. HUNTER: This organism was resistant to penicillin, a characteristic rather typical of the enterococci as a class. Organisms which are not inhibited by 10 to 20 units of penicillin may be classed as highly resistant. Most of the non-hemolytic streptococci which are recovered from cases of bacterial endocarditis are sensitive to about one-tenth of a unit of penicillin. Thus this organism was probably one hundred times as resistant as the usual sensitive organism encountered. It was not, however, completely resistant to penicillin in a range that may be obtained with extremely high doses of the drug.

In contrast, the organism was extremely sensitive to aureomycin. It is very difficult to interpret the aureomycin sensitivity of a given organism in terms of desired dosage. Aureomycin is unstable at 37°c. and deteriorates as the sensitivity test is run. This fact must be kept in mind when one interprets the results. For example, the determination cited in the protocol was read at four hours. In our laboratory where we read the test at twenty-four hours, the figure was not as low. However, one can say that the organism was quite susceptible to aureomycin and moderately susceptible to chloromycetin. It was resistant to streptomycin.

DR. HARFORD: In regard to the determination of antibiotic sensitivity it should be pointed out that the methods are rather crude and the correlation between *in vitro* determination and *in vivo* results may be somewhat variable. Therefore, it is important to overshoot the mark. One should not attempt to obtain a blood level just above that to which the organism is sensitive *in vitro*.

DR. HUNTER: I agree, in general, with Dr. Harford's comments; I think that the determination of sensitivity is extremely helpful, however, and gives the physician an idea as to the order of magnitude of antibiotic dosage which must be used.

DR. ALEXANDER: At one time the patient's aureomycin blood level reached a value of 160 gamma. Do you have any comments to make on the optimal blood level of aureomycin in the treatment of bacterial endocarditis?

DR. HUNTER: There is no information available as to the desired level of aureomycin in this disease. Little experience in the treatment of bacterial endocarditis with aureomycin has been accumulated. Certainly the levels ordinarily obtained would be much lower than those reported here and probably a level between 5 and 20 micrograms would be satisfactory. The fact that this patient had renal insufficiency probably contributed to the high blood level.

DR. ALEXANDER: What are the toxic effects of aureomycin?

DR. HUNTER: There are very few reported and no particularly serious ones. Aside from the various gastrointestinal complaints, chiefly nausea and vomiting, I know of no serious effects. There is no evidence of hepatic damage arising as a result of aureomycin therapy.

DR. HARFORD: There is one report in the literature of patients with Hodgkin's disease who were given as much as 4 gm. of aureomycin intravenously a day. Liver and kidney function tests in this group were normal.

DR. ALEXANDER: Why did this patient develop jaundice, Dr. Shank?

DR. ROBERT E. SHANK: Several possibilities must be considered. The patient had been ill for some time and had been treated by a number of physicians. He received a number of injections and he certainly had been bled. Therefore, it is conceivable that he may have had viral hepatitis of the homologous serum type.

He also may have had viral epidemic hepatitis. The liver function tests done in this hospital indicated parenchymal damage, but they do not enable one to define exactly the nature of the lesion.

DR. HUNTER: A certain number of patients with bacterial endocarditis, whether or not they develop jaundice, show some evidence of liver damage such as an abnormal cephalin-cholesterol flocculation test or a slight rise in alkaline phosphatase. There may also be changes in the serum protein. Jaundice, however, is uncommon.

DR. ALEXANDER: Why was no urobilinogen found in the patient's urine, Dr. Shank?

DR. SHANK: It has been reported that when aureomycin is given by the oral route, organisms in the gastrointestinal tract which are responsible for the conversion of bilirubin to urobilinogen are inhibited or destroyed; consequently the conversion does not occur. Such an explanation is quite likely in this instance.

DR. ALEXANDER: Would you comment on the pulmonary findings, Dr. Goldman?

DR. ALFRED GOLDMAN: Embolic phenomena, of course, arise in bacterial endocarditis but, so far as we know, the patient had no lesion in the right side of his heart and consequently that explanation would not hold here. The x-ray findings were suggestive of atelectasis; pneumonitis must also be considered.

DR. ALEXANDER: One must also consider a pulmonary infarct.

DR. WOOD: If the patient had thrombophlebitis in the leg veins, Dr. Alexander, and then developed pulmonary embolism, another explanation of the jaundice could be put forward for pulmonary infarction is not infrequently accompanied by the jaundice.

DR. CHARLTON DE SAUSSURE: Do you believe that the serum bilirubin is apt to rise to as a high a level as was seen here in pulmonary infarct?

DR. WOOD: That would be unlikely. It is also possible that a hemolytic reaction resulted from one of the blood transfusions but the sodium bilirubinate level is much too high to be explained either by the jaundice of pulmonary infarction or hemolysis following transfusion.

DR. GUSTAVE J. DAMMIN: The threshold to excretion of sodium bilirubinate develops rapidly and negative tests for urinary bile have been recorded when the sodium bilirubinate level was over 3.0 mg. per cent; in an acute episode such as this one, however, it is difficult to understand why bile was not found in the urine.

DR. WOOD: Perhaps renal insufficiency played a part in the phenomenon.

DR. ALEXANDER: Dr. Massie, did this patient die of cardiac failure?

DR. MASSIE: I would hesitate to say that he died of heart failure *per se*. I would not be able to suggest any specific cause for death.

DR. ALEXANDER: The patient's non-protein nitrogen was 125, he had red cells and red cell casts in his urine and he was somewhat obtunded. Is it possible that he died of renal failure, Dr. Schroeder?

DR. HENRY A. SCHROEDER: Certainly uremia could have been a contributory factor.

DR. ALEXANDER: Do you think the patient was cured of bacterial endocarditis, Dr. Hunter?

DR. HUNTER: I am afraid I do not know.

DR. ALEXANDER: If one successfully treats a patient with bacterial endocarditis who has developed azotemia, does the renal damage persist?

DR. HUNTER: That is variable. Some patients with evidence of marked renal damage resulting from bacterial endocarditis improve dramatically after the infection is cured and their renal function returns nearly or completely to normal. Others have died of renal insufficiency despite cure of the infection.

DR. WOOD: The patient's serum chloride level rose to 125 mEq./L. and there is only one situation which comes to my mind which satisfactorily explains that level, namely, a lesion in the pancreas. I believe, therefore, that it is conceivable that the patient died of acute pancreatitis.

DR. ALEXANDER: In summary, I believe that we would all agree that this patient had subacute bacterial endocarditis presumably engrafted on the valvular lesions of rheumatic heart disease, primarily the aortic valve. He possibly had a pulmonary infarction or pneumonitis but the nature of the hepatic lesion is not clear. Epidemic viral hepatitis or homologous serum jaundice have been mentioned as possibilities. Finally, Dr. Wood suggests acute pancreatitis as a terminal episode.

Clinical Diagnosis: Subacute bacterial endocarditis due to Streptococcus liquefaciens (enterococcus); rheumatic heart disease with aortic insufficiency and mitral stenosis; hepatitis, ? epidemic or homologous serum type; ? pulmonary infarct; ? pneumonitis; ? acute pancreatitis.

PATHOLOGIC DISCUSSION

DR. J. C. ROBERTS: Icterus was no longer apparent at the time of the autopsy. The lungs were slightly edematous and congested and there were indistinctly outlined, firm, nodular foci typical of bronchopneumonia in the lower lobe of the left lung. There was no fluid in either pleural cavity.

The heart was slightly larger than normal, weighing 400 gm. The endocardium of the left atrium was yellow-grey and slightly thickened. Immediately above the edges of the leaflets of the mitral valve there were firm, rolled, nodular thickenings. The chordae tendinae were slightly thickened. Grey-yellow calcified masses in the bases of the cusps of the aortic valve were noted, and fine adhesions were present at the commissures. The center of the posterior cusp was replaced by reddish brown, friable, granular material about a rupture which had reduced the cusp to two large lateral pieces attached at the base and lateral margins, and a small central piece attached only at the base. There were small foci of the same type of friable vegetation on the right anterior cusp in the region of the corpora aranti. Five millimeters above the posterior cusp on the surface of the aorta, and below the posterior cusp, on the ventricular aspect of the base of the anterior leaflet of the mitral valve, there were similar vegetations. There were no lesions on the right side of the heart.

On opening the peritoneal cavity about 200 cc. of reddish brown, opaque, slightly turbid fluid were present. The surfaces of the peritoneal cavity were dull and slightly granular. The normal architecture of the tail of the pancreas was obliterated by red-purple, soft, gelatinous material which extended into the peripancreatic tissue and involved the lower pole of the left adrenal. This process also involved the hilum of the spleen which was adherent to the tail of the pancreas. The remainder of the pancreas was slightly and diffusely reddened. The major pancreatic ducts were all patent and not dilated. No calculi were found and the ampulla of Vater was patent. The splenic artery and its pancreatic branches contained no thrombi.

The liver was of normal size and had a diffuse yellow-brown tinge on the cut surface. The centers of the lobules were red-grey, but there were no gross lesions in either the liver or biliary ducts. The kidneys were of normal weight. There were old infarcts in the lower poles of both kidneys. The cortical surfaces were diffusely and regularly granular and there were many small petechiae in the cortex. In the upper third of the right ureter there was a compact, brown, granular calculus 1 cm. in diameter that completely occluded the ureter. The mucosa of the proximal ureter and the lower pelvis was thickened but there was no significant dilatation of those structures or atrophy of the kidney.

In the spleen there was an old subcapsular infarct which involved about one-fifth of the total parenchyma. There were occasional petechiae in the mucosa of all portions of the gastrointestinal tract. In the terminal ileum, cecum and rectosigmoid colon the mucosa was red-purple and velvety without ulcerations. In the brain there were two small, yellow, soft foci confined to the cortex of the temporal lobe and the Island of Reil on the right.

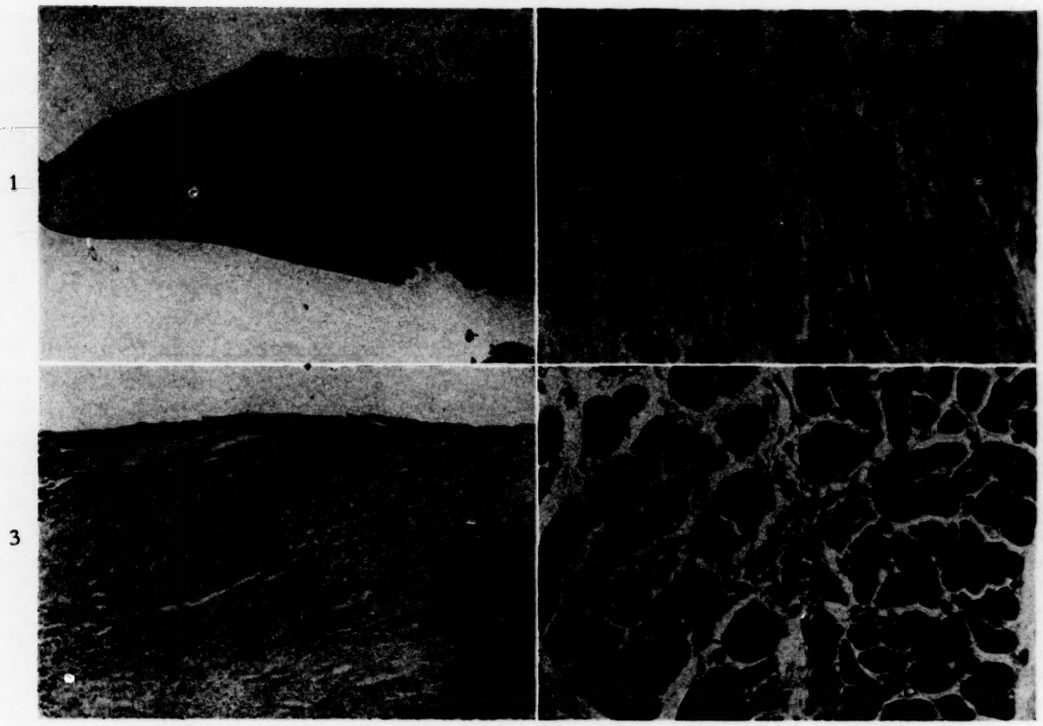


FIG. 1. An active vegetation of subacute bacterial endocarditis on the posterior leaflet of the aortic valve; the base of the cusp is on the left side of the section.
FIG. 2. Viable streptococci within and about cells in the vegetation.
FIG. 3. A zone of partial healing at the edge of a vegetation on the mitral valve.
FIG. 4. Focal cellular infiltration about a capillary in the myocardium; these are the Bracht-Wächter bodies, a microscopic embolic phenomenon of subacute bacterial endocarditis.

DR. ROBERT A. MOORE: This patient had subacute bacterial endocarditis involving the aortic valve and adjacent structures, and associated with infarcts in the spleen, kidneys and one part of the brain. In addition there was a renal calculus which totally occluded the right ureter and acute hemorrhagic necrosis of the tail of the pancreas.

Figure 1 illustrates a section of the greater part of the posterior leaflet of the aortic valve. On the left side the essentially unaffected portion of the valve is seen and at the right the margin with the vegetation. There are large numbers of bacterial colonies and little evidence of healing apparent at this magnification. In Figure 2, at higher magnification, is a section stained for bacteria; individual cocci were in intimate association with living cells. Many of these bacteria were within cells and from a histologic standpoint appeared to have established a symbiotic relation to them. An organism identical to that isolated from the blood during life was obtained by culture of this tissue. Figure 3 is from a section of the mitral valve adjacent to an acute vegetation similar to that on the aortic valve. In the center of the illustration are small deposits of calcium and there is proliferation of tissue on the surface of the valve indicating some degree of healing. This degree of response in the valve was no greater than that which was often seen in subacute bacterial endocarditis before the advent of specific antibiotic therapy. That does not mean that the therapy in this case was entirely without effect, but only that the healing present was not sufficient to distinguish it from the type of healing which can be expected when this disease lasts for a considerable period of time.

Figure 4 is a section of the myocardium which contained a few leukocytes and

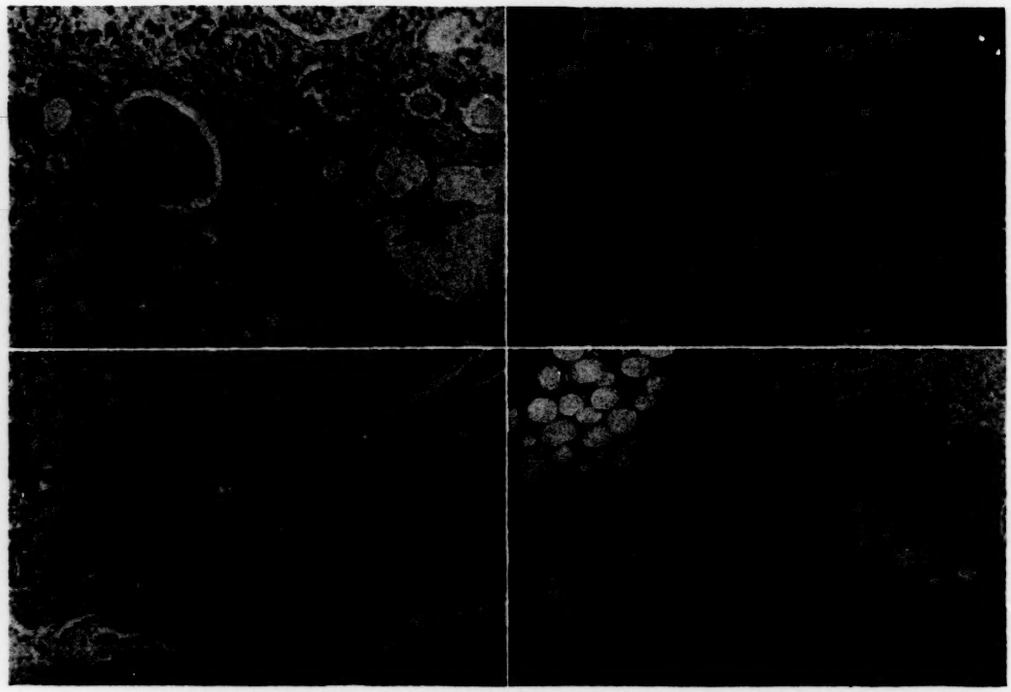


FIG. 5. A healed, partially infarcted glomerulus in the kidney which has resulted from focal embolic glomerulonephritis; there are also edema of the interstitial tissue and dilatation of the tubules in this field.

FIG. 6. A very low magnification of a section of the liver in which a slight increase of periportal tissue, slight fatty metamorphosis and central atrophy are apparent.

FIG. 7. Squamous metaplasia of the epithelium with almost complete occlusion of a duct in the head of the pancreas.

FIG. 8. A focus of acute hemorrhagic necrosis in the tail of the pancreas with a thrombus in an involved vein.

mononuclear cells around a capillary. This type of microscopic embolic lesion is characteristic of this disease and corresponds to similar embolic foci often present in other parts of the body. Such foci contain no suppuration or necrosis and consist only of cellular infiltration. In other portions of the myocardium there was a little perivascular fibrosis. The degree of coronary arteriosclerosis was not sufficient to account for this lesion. It might, therefore, be related to the subacute bacterial endocarditis or to rheumatic fever, although I must point out there was very little other anatomic evidence of rheumatic fever. The mitral and aortic valves were slightly thickened, but those changes could have developed in response to subacute bacterial endocarditis if it were present for the five or six months since this patient underwent cystoscopy or the extraction of teeth. There were no changes in the pericardium, no adhesions and no thickening of the epicardium of the heart. The focal fibrosis around the vessels in the myocardium was, therefore, the only objective finding suggestive of past rheumatic fever; that evidence seems of little importance in relation to the migratory joint pains the patient was said to have experienced forty-five years before.

Figure 5 is from the kidney and is a beautiful example of healed focal embolic glomerulonephritis. One lobule of the glomerulus to the left of the center of the field had been destroyed and replaced by fibrous tissue. Other changes in this kidney were fairly extensive. There was only a mild degree of nephrosclerosis, of insufficient degree to have had much effect on the patient's course. There were also distinct interstitial edema, some interstitial fibrosis, dilatation of tubules, and in some of the

tubules red blood cell and hemoglobin casts out of proportion to the degree of focal embolic glomerulonephritis. All of the glomeruli in this kidney contained swollen endothelial cells indicative of acute widespread glomerulitis which might be interpreted as early, slight glomerulonephritis; such response is not unusual in the presence of an infection such as subacute bacterial endocarditis. The hemoglobin casts with red blood cells were suggestive of a transfusion reaction, particularly as the patient was known to have developed jaundice in the course of his illness, but there was no evidence other than the hemoglobin casts which could not be accounted for on the basis of the glomerular damage.

In Figure 6 a slight increase of fibrous tissue in the portal spaces of the liver was apparent. There was also widespread but slight fatty metamorphosis of the liver and distinct congestion with some central atrophy of hepatic cells. The cause of the episode of jaundice was not explained by the relatively insignificant changes in the liver, although many bile canaliculi were filled with inspissated bile suggesting that the obstructive features indicated by the clinical tests of hepatic function arose on an intrahepatic basis. There were no lesions in other organs such as infarcts of the lung or pneumonia of sufficient duration to provide an explanation of the jaundice. The bronchopneumonia present at the time of death was of slight extent and acute character.

In the center of Figure 7 there is a duct from the head of the pancreas in which there is a striking example of squamous metaplasia of the ductile epithelium. This lesion has been postulated to be one of the more common mechanisms by which the pancreatic ducts can be occluded or partially occluded to initiate hemorrhagic necrosis of the pancreas.

Figure 8 is an illustration of a section of the tail of the pancreas in which there was a large focus of typical necrosis of the pancreatic and surrounding adipose tissue associated with thrombi in the veins and intact arteries. This picture is characteristic of acute hemorrhagic necrosis of the pancreas associated with squamous metaplasia of the ducts, a lesion adequately and fully described by Rich and Duff* a number of years ago. They postulated that the initial lesion is obstruction of the pancreatic ducts, followed by acute hypersecretion such as might be induced by acute alcoholism or by the taking of food which results in rupture of the small pancreatic ducts behind the partial or total occlusion and consequent release of the pancreatic ferments into the interstitial tissue. A specimen of serum taken by Dr. Roberts at the time of autopsy contained 3,700 units of amylase activity per 100 cc. and a sample of the hemorrhagic ascitic fluid contained 50 units per 100 cc. The terminal changes observed in the electrocardiogram are of the nature that have been described in acute hemorrhagic necrosis of the pancreas and may well have been due to that lesion.

The patient's history of renal colic is well explained by the stone which totally occluded the right ureter. This finding constitutes a good example of the fact that hydronephrosis does not occur when the ureter is totally occluded in contradistinction to the result of temporary or intermittent obstruction of the ureter. The obstruction in this case was not of sufficient duration to cause atrophy of the kidney. There was nothing in the lungs to account for the history of hemoptysis fourteen years before the patient's death. The left femoral artery contained no occlusion but the examination was not extended below the thigh.

DR. HUNTER: This case was of extraordinary interest from the point of view of therapy in bacterial endocarditis. This patient had aureomycin in doses that resulted in levels in the blood greatly in excess of the inhibitory level for weeks, and yet there is no evidence that significant healing of the vegetation took place. We know that clinical remissions and negative

* RICH, A. R. and DUFF, G. L. Experimental and pathological studies on the pathogenesis of acute hemorrhagic pancreatitis. *Bull. Johns Hopkins Hosp.*, 58: 212–259, 1936.

blood cultures can be produced in bacterial endocarditis with doses of antibiotics which do not cure. The fact that aureomycin is a bacteriostitic but not a bactericidal agent may account for the failure here. This situation is comparable with the experience with other bacteriostatic agents used in the treatment of this disease—witness the sulfonamides. I think that these factors indicate that aureomycin may be of limited value in this disease, although a few cures have been reported with this agent alone.

Final Anatomic Diagnoses: Subacute bacterial endocarditis involving the right coronary and posterior cusps of the aortic valve (Streptococcus liquefaciens); focal embolic glomerulonephritis; squamous metaplasia of the pancreatic ducts in the head of the pancreas; hemorrhagic necrosis of the pancreas.

Acknowledgement: Photographs were made by the Department of Illustration, Washington University School of Medicine.

Special Feature

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE SEVENTH ANNUAL MEETING OF THE MIDWESTERN SECTION HELD IN CHICAGO, NOVEMBER 3, 1949

CLINICAL APPRAISAL OF THIOMERIN, A NEW MERCURIAL DIURETIC. *Jonathan Slomowitz, M.D. (by invitation) and Francis F. Rosenbaum, M.D. Milwaukee, Wis.*

The latest in a series of mercurial diuretics to be introduced is thiomerin. The advantages of lessened cardiac toxicity and painlessness on subcutaneous injection are claimed for it. Favorable experience with this preparation has been reported by several observers. The purpose of this study was to evaluate this drug in both hospitalized and ambulatory patients and to compare it with the other mercurial diuretics in common use.

Thiomerin was given to forty-two patients in the hospital; each patient received multiple injections either intravenously, intramuscularly or subcutaneously. In the majority the latter route was used. Diuresis was determined by measuring weight loss. The responses were satisfactory in thirty-seven patients; failures occurred in five patients. Two individuals had pain at the site of subcutaneous injection. Fatal lower nephron nephrosis developed in an aged, chronically ill woman after the accidental intravenous administration of 10 cc. of thiomerin despite prompt treatment with BAL. No other untoward reactions occurred. Thiomerin was found to be as effective as the other mercurial diuretics in common use. In rare instances diuresis occurred after thiomerin when other diuretics failed and in other patients the reverse was true.

Thiomerin was used in eight patients in the outpatient cardiac clinic for a total of 152 doses to test the feasibility of subcutaneous self-administration. Although the group was limited in number, this plan seemed practical. In two of these patients a fine macular eruption appeared on the arms and hands.

TECHNIC OF TREATING MYELOGENOUS LEUKEMIA WITH RADIOACTIVE PHOSPHORUS. *George V. LeRoy, M.D. and Wilbur R. Tweedy, Ph.D. Chicago, Ill.*

Controlled therapy of leukemia with P^{32} is possible if one knows the amount of the administered dose which remains in the body during the period of treatment. Average rate of excretion of P^{32} is 15 per cent of the dose per week. Of the remaining P^{32} 29 per cent per week undergoes radioactive decay and this amount represents the beta radiation which is available for treatment. In a study of twenty-nine patients it was found that the amount of radiation which produced a satisfactory remission was equivalent to 1.6 mc. to 2.0 mc. per week. Dosage schedules which will provide this amount are as follows:

Dose Desired (mc./wk.)	Initial Dose (mc.)	Weekly Maintenance Dose (mc.)
1.300	5.0	2.0
1.500	6.0	2.4
1.800	7.0	2.8
2.000	8.0	3.2

Using this technic of therapy it has been possible to treat myeloid leukemia in a controlled manner and to produce remissions which are quite similar to those induced by roentgen therapy.

EFFECT OF A DEPOT HEPARIN PREPARATION ON THE BLOOD-CLOTTING MECHANISM. *Ivan F. Duff, M.D., Thomas Kay Buchanan, M.D. and James W. Liman, M.D. (by invitation). Ann Arbor, Mich.*

The effect on clotting time (Lee-White) of two preparations designed to prolong action and facilitate administration of heparin has been observed on forty-seven occasions in twenty subjects with and without thromboembolism. Heparin sodium in an aqueous vehicle of gelatin and dextrose was given by deep subcutaneous or intramuscular injection; the second preparation contained, in addition, epinephrine and ephredrine as vasoconstrictors. Minor local discomfort

for twenty-four to forty-eight hours was common; in three cases there was pain and limping and local ecchymosis developed in one patient.

A two-fold increase in clotting time following a single injection was considered an adequate effect. Single injections of 300 to 400 mg. (with or without vasoconstrictors) produced an adequate heparin effect. In 75 per cent 200 mg. doses produced an adequate effect; 50 to 100 mg. doses proved ineffective. Clotting times up to one and a half hours were seen. With few exceptions an adequate effect was obtained 3.3 to 5.6 hours after injection of 200 to 400 mg. indicating that an emergency state of thromboembolism may require initial intravenous heparin. Duration of adequate effect ranged from four to eighteen hours never exceeding thirty-two hours. Circulating heparin may be dramatically neutralized within thirty seconds by intravenous protamine sulfate; in a few hours the clotting time may revert to its former high level. Prolongation of the clotting time by heparin may be associated with marked increase in the prothrombin time.

ALTERATION OF BLOOD PROTHROMBIN CONCENTRATION FOLLOWING BURNS. *Louis T. Gabriel, M.D., Donald E. Van Hoek, M.D., Simon Kalish, A.B. (by invitation) and Darrell A. Campbell, M.D. Eloise, Mich.*

An investigation of the effect of thermal burns on individual blood coagulation factors revealed interesting changes in blood prothrombin concentration. In eight dogs that survived the seven-day period of observation following severe thermal burns the prothrombin concentration, as determined by the two-stage method, was slightly elevated in the first twenty-four hours and then exhibited a gradual decline. The lowest levels were observed on the seventh day at which time the mean fall was 16 per cent. In marked contrast, four animals that failed to survive demonstrated a precipitous fall in the first twenty-four hours, the maximum drop noted being 58 per cent observed at four hours.

These findings parallel those of Lockwood who noted in animals that failed to survive a fall in prothrombin level within twenty-four hours after operation performed for the purpose of inducing experimental peritonitis. He concluded that the stability of the prothrombin level in the first twenty-four hours is a reliable prognostic sign.

It was anticipated that the gradual decline in prothrombin level noted in the surviving dogs would continue. This was confirmed by the demonstration of hypoprothrombinemia in four previously healthy human patients who, despite the administration of repeated whole blood transfusions in the course of treatment for severe burns, were found to have blood prothrombin concentrations of only 44, 44, 47 and 50 per cent on the twenty-fifth, fortieth, fifty-third and 121st post-burn days. Further investigation of this problem may show anticoagulants to be contraindicated in the treatment of severely burned patients.

CHANGES IN PLASMA VOLUME, SERUM PROTEIN CONCENTRATIONS AND TOTAL CIRCULATING PROTEINS FOLLOWING THE REMOVAL OF ASCITIC FLUID FROM PATIENTS WITH LAENNEC'S CIRRHOSIS. *Glenn I. Hiller, M.D., Elston R. Huffman, M.D. and Stanley Levey, Ph.D. Eloise, Mich.*

Plasma volume (T-1824), serum protein concentrations and total circulating proteins were determined in seven instances before, immediately after and eight hours following the complete removal of ascitic fluid from five patients with advanced Laennec's cirrhosis of the liver. In all instances immediately following the removal of ascitic fluid the plasma volume, total circulating protein and total circulating globulin fell, the maximum fall being 25, 29 and 31 per cent, respectively, of the control values. In four instances the total circulating albumin rose. Concentrations of the various serum proteins immediately after the paracenteses exhibited no consistent deviation, being either above or below the control values.

Eight hours following the paracenteses the values for plasma volume revealed no consistent pattern. Both significant elevations and decreases were encountered while others returned to approximate control levels. In most instances total circulating protein, total circulating globulin and total protein concentrations were appreciably lowered. Total circulating albumin and the albumin and globulin concentrations exhibited no consistent deviation, being either above or below control values eight hours following the paracenteses.

These data suggest (1) that the circulating plasma volume falls, without appreciable hemoconcentration, immediately after the removal of ascitic fluid, (2) that even in the advanced cirrhotic albumin stores are available, (3) that routine serum protein concentrations should not be obtained on the same day that ascitic fluid

is removed and (4) an explanation for the peripheral vasomotor collapse encountered in the occasional patient following the too rapid removal of ascitic fluid.

HEMODILUTION AS A RESULT OF ESTROGEN THERAPY. *Carroll L. Witten, M.D. (by invitation) and James T. Bradbury, Sc.D. Louisville, Ky.*

Clinical findings have suggested the possibility that estrogens have a definite effect on blood and its peripheral distribution in women. Red blood cell counts, hematocrit and hemoglobin determinations were made on alternate days before, during and after estrogen therapy. Estrone (theelin, aqueous 5 mg.) or estradiol dipropionate (diovocylin 0.4 mg.) was given on alternate days for three or four injections to ten and four women, respectively. There was consistently a decrease in the red blood cell count (5 to 25 per cent), hematocrit (5 to 23 per cent) and hemoglobin (4 to 15 per cent). The decrease was evident at the time of the second injection and the maximal effect was recorded two or three days after the last injection. These findings indicated hemodilution. Evans blue T 1824 was used and it was found that the plasma volume increased as much as 21 per cent as a result of estrogen treatment. After cessation of therapy the blood findings returned to or above the original values in about ten days.

SOME ACCOMPANIMENTS OF RAPID DEHYDRATION IN THE TREATMENT OF CONGESTIVE HEART FAILURE, PARTICULARLY IN CONNECTION WITH THE PRODUCTION OF THROMBOEMBOLIC PHENOMENA. *R. J. Marvel, M.D. (by invitation) and Wendell A. Shullenberger, M.D.*

Fourteen patients admitted in congestive heart failure to the Indianapolis General Hospital were uniformly treated with an intensive regimen of sodium restriction, mercurial diuretics and digitoxin. The digitoxin was withheld in two cases. Before treatment and during diuresis a period averaging about two weeks, frequent determinations of hematocrit, prothrombin time, plasma fibrinogen, coagulation time (Lee and White), clot retraction and albumin-globulin ratio were made. Liver profiles were done at the beginning and end of treatment.

Prothrombin behavior did not adhere to any definite pattern but an average of curves from all patients rose from 60 to 84 per cent during the period of diuresis. The average of hematocrit curves rose from forty-seven volumes per cent to fifty-four volumes per cent during the same period. Mean behavior of prothrombin and hematocrit does not reflect the rather abrupt increases which were observed in individual cases. The other observations relative to thrombus formation showed rather violent fluctuation but in most cases there was at least one time at which combination of factors theoretically favored thrombosis.

Chest films on admission, reviewed with the radiologist, suggested pulmonary embolism in six cases. During diuresis, plantar vein thrombosis appeared in one patient and saphenous thrombosis in two, one of which had received no digitalis. Prothrombin determinations at these times were 90, 66 and 47 per cent but there were hematocrit increases averaging seven volumes per cent above the pretreatment levels.

Two patients without heart disease, subjected to the regimen, showed hematocrit increases but no disturbance in prothrombin or other factors studied.

EXPERIMENTAL STUDIES ON THE REINNERVATION OF MUSCLES AFTER THE REPAIR OF PERIPHERAL NERVES BY END-TO-END SUTURES, AUTOGENOUS AND HOMOGENOUS GRAFTS. *George Perret, M.D. Iowa City, Ia.*

Studies of the gastrocnemius muscle of 101 cats were made from six to 980 days following primary repair of the sciatic nerve with end-to-end sutures, autogenous and homogenous grafts.

The rate and quality of muscle reinnervation was most satisfactory following end-to-end suture and was delayed after the use of grafts by the internal organization and the innervation of the graft itself. It was more rapid and more satisfactory in the cases of autografts which had preserved their original neurilemal structure than in the cases of homografts which had undergone necrosis and fibrotic organization. Muscle contractions could be obtained by electrical stimulation of the nerve fifteen days after beginning muscle innervation while spontaneous muscle function appeared much later.

Most of the regenerating nerve fibers followed the old nerve pathways leading to the motor end-plates and made contact with the old well preserved end-plate nuclei and anomalous end-plate innervation was rare. End-plates that were not reinnervated were noted especially after longer periods of denervation, more frequent following nerve repair with homografts.

Atrophy, present in all denervated muscles, recovered very slowly after muscle reinnervation. Muscle contractures developed in many cases during the period of muscle denervation, they impaired normal return of function and increased the degree and period of atrophy.

Muscle recovery depends upon the quick return of regenerating nerve fibers into the motor end-plates. The longer the period of denervation the more severe is the atrophy and the ensuing fibrosis in the distal nerve as well as the muscle. Early nerve repair is essential and justifies the use of grafts if immediate end-to-end suture is not possible. The discrepancy between satisfactory nerve regeneration and poor functional recovery is thought to be due to disuse atrophy resulting from contractures, pain or other sensory disturbances and to cross innervation by nerve fibers originally destined to antagonistic muscles. Therefore, early and prolonged physiotherapy and muscle re-education are found essential to improve functional recovery.

EFFECT OF DIGITALIS IN PATIENTS WITH ENLARGED HEARTS AND SINUS RHYTHM BUT WITHOUT CONGESTIVE FAILURE. *Joseph M. Ryan, M.D. (by invitation) and Henry A. Zimmerman, M.D. Cleveland, O.*

Christian first advocated digitalization of patients with enlarged hearts before failure. Stewart, using the acetylene gas method, studied cardiac outputs in patients with large hearts and no congestive failure. Some patients had an increased cardiac output, some a decreased output and some had no change in cardiac output. There was no change in the venous pressure. Cournand reported that large hearts of arteriosclerotic and rheumatic etiology, with no congestive failure, when given digoxin had a decrease in cardiac output.

We studied cardiac outputs by the direct Fick principle in eight patients with enlarged hearts and sinus rhythm but no congestive failure (determined not only clinically but by appraisal of the right auricle pressure and the right ventricle diastolic pressure). Three had hypertensive heart disease, one had rheumatic heart disease, two had cor pulmonale, one luetic aortic insufficiency and one coronary artery disease. In all these patients the cardiac outputs, the right auricular pressures and the right ventricular diastolic pressures were with normal range. After rapid digitalization followed by a maintenance dose of whole leaf the cardiac output was increased significantly in one patient and remained essentially the same in seven. There was no consistent change in the right auricular mean pressure. The pulmonary artery, femoral artery and right ventricular pressures, the heart rate, stroke volume and A-V oxygen differences remained essentially unchanged.

DIAGNOSIS OF POSTERIOR MYOCARDIAL INFARCTION WITH THE AID OF SEMIDIRECT LEADS FROM THE BACK AND ESOPHAGUS. *Charles H. Sears, M.D. (by invitation) and Gordon B. Myers, M.D. Detroit, Mich.*

Large posterior myocardial infarcts may produce no diagnostic signs in standard leads and aV_F when the heart is in horizontal position. Infarcts confined to the basal portion of the posterior wall may be undetectable in these leads even though left ventricular potentials are referred to the diaphragm.

The purpose of this study was to determine whether or not semidirect leads from the back would be of aid in the diagnosis of posterior infarction. The following nine back leads were obtained, namely, V_7, V_8, V_9 taken in the same transverse plane as V_5, V_6, HV_7, HV_8, HV_9 taken at the horizontal level at the junction of the third interspace and sternum and LV_7, LV_8, LV_9 taken at the level of the twelfth rib.

These leads were obtained in twenty-five controls, in thirty-six patients with definite evidence of posterior infarction established either by autopsy or esophageal leads and in twelve additional patients in whom posterior infarction was established by previous serial electrocardiograms.

The QRS-T pattern in the back leads has been correlated with that in the esophageal leads and in aV_F. Back leads were of aid in recognition and in estimation of the extent of the posterior infarct in many cases but failed to show definite signs of infarction in a few cases in which esophageal leads were positive.

Electrocardiograms will be presented to illustrate the pattern in esophageal and back leads in normal controls, extensive posterior and posterolateral infarction and in localized posterobasal, posteroapical, posteroseptal lesions.

ENDOCRINE SIGNIFICANCE OF LEUKOCYTE PATTERNS DURING ACUTE GOUTY ARTHRITIS. *Wm. Q. Wolfson, M.D. and Clarence Cohn, M.D. Chicago, Ill.*

Because of their endocrine significance leukocyte patterns in acute gouty arthritis have been reinvestigated. Previous investigators have re-

ported monocytosis and increased immaturity of polymorphonuclears. Occurrence of relative polymorphonuclear leukocytosis has frequently been stated to occur but without supporting data.

In one group of patients erythrocyte sedimentation rate (ESR) was used as the criterion of arthritic activity. Eosinopenia and lymphopenia did not occur as ESR increased. Instead, the total white count increased due to proportionate increases in each of its constituents. Absolute monocyte counts were somewhat above normal both during interval gout and attacks. The reported increased immaturity of polymorphonuclears was confirmed.

In a second series total leukocyte counts and direct eosinophil counts (modified Randolph technic) were studied in the same patients during both interval and attack phases. During the interval total leukocytes averaged 7,567 with 156 eosinophils. During attacks total leukocytes averaged 9,545 with 210 eosinophils. Qualitative normality of the eosinophils present during attacks was shown by normal eosinopenic responses to administered ACTH.

These findings permit the following deductions. First, the adrenal cortex remains responsive to ACTH during acute gouty arthritis and eosinopenia in response to glycocorticoid output (lymphopenia, eosinopenia, relative polymorphonuclear leukocytosis) during the attack indicates that the stress of an acute gouty attack does not adequately excite the hypothalamic-pituitary mechanism to increase the rate of ACTH release. Second, the proportionate increase in all leukocyte types noted during acute gouty arthritis must arise from a general increase in the rate of leukocyte production, a general decrease in the rate of leukocyte destruction or from hemoconcentration. The increased immaturity of the polymorphonuclear leukocytes perhaps favors the first of these possibilities.

HUGGINS' TEST FOR CANCER: REPORT OF 250 PROCEDURES. *J. L. Eisaman, M.D., L. E. Schneider, M.D. (by invitation) and R. E. Berger, M.Sc. (by invitation) Bluffton, Ind.*

A series of 250 Huggins' tests (least coagulable protein concentration) was performed on 239 patients. Seventy-seven of these patients had a pathologic diagnosis of cancer at some time. Of this number the Huggins' test gave negative results in 110 patients in whom no evidence of cancer could be found. The positive test in known cases of cancer included carcinomas of almost every organ and one lymphosarcoma; negative results ran the gamut of general hospital diagnoses. These included chronic diseases often encountered in the cancer age.

Of the thirty-seven patients with known cancer and negative Huggins' results eight had gastrointestinal malignancies. Three tests on two different patients were definite failures, negative before operation and in both cases becoming positive during the week following surgery. The other negative cases were from four months to two years postoperative without clinical evidence of recurrence.

False negatives were encountered in breast cancer (1), prostatic cancer (1), Hodgkin's disease (1), retinoblastoma (1), malignant melanoma (1), sarcoma (1), hemangioblastoma (1) and metastatic carcinoma of lymph nodes (1). There were no proven false negatives in ten cancers involving the bladder (2), skin and orifices (5) and ovary (3).

Negative tests in cancer cases occurred from two months to eighty-two months postoperatively. The longest negative test case was a twenty-two year post-irradiation skin cancer. Apparent false positive results were obtained in a variety of conditions, prominent among which were arthritides, thyroid diseases, mazoplasia, duodenal ulcers and gastritides.

CLINICAL STUDY OF SUPERIOR VENA CAVAL OBSTRUCTION. *Malcolm McCord, M.D. (by invitation), Philip Edlin, M.D. (by invitation) and Malcolm Block, M.D. Dayton, O.*

Ten cases of obstruction of the superior vena caval system observed in a general hospital during the course of one year are presented. It is believed that the incidence of this syndrome is considerably higher than is stated in the literature.

In addition to clinical studies four of these patients had postmortem examinations and six had venographic studies. The diagnosis was suspected in cases showing a mediastinal mass, edema of the upper body or visible venous distention of the upper body with or without collateral formation. In those cases in which caval obstruction was suspected, venous pressure determinations were done to demonstrate elevation in the arms with normal levels in the legs and a significant elevation of the venous pressure in the arm on hand exercise. Visualization by venograms was then obtained. A block was identified by a constant defect on serial

films, marked collateral venous pattern and retention of opaque media distal to the point of obstruction. The abnormal venous pathways were most accurately demonstrated by simultaneous injection of radio-opaque material into the veins of both arms.

In the studied cases obstruction was caused by aneurysm (4), bronchogenic carcinoma (3), mediastinal lymphoma (1), thrombosis secondary to cardiac failure (1), thrombosis secondary to trauma (1), chronic mediastinitis (1) and tension pneumo-thorax (1).

DIRECT BLOOD PRESSURE DETERMINATIONS AND COMPARATIVE ARM BLOOD FLOWS IN SUBJECTS WITH COARCTATION OF THE AORTA, THE STRICTURE BEING PROXIMAL TO ORIGIN OF LEFT SUBCLAVIAN ARTERY. *Howard B. Burchell, M.D., Bowen E. Taylor, M.D., J. R. B. Knutson, M.D. and Khalil G. Wakim, M.D. (by invitation) Rochester, Minn.*

Two patients, fourteen and fifty-three years old, have been studied who are believed to have a coarctation proximal to the origin of the left subclavian artery. Neither had symptoms of arterial insufficiency in the left arm; both were accustomed to hard manual work. Blood pressures were measured simultaneously by strain gages attached to intra-arterial needles in the right radial, left radial and one of the femoral arteries.

In the first case the systolic and diastolic pressures were 157/69, 90/68, 110/66 and in the second case 230/70, 79/57 and 111/65 mm. Hg, respectively. The pulse contour in the left radial artery was a close replica of that obtained in the femoral artery in each case. Plethysmographic determinations of the blood flow in the arms showed a greater flow in the right than in the left.

With reflex vasodilatation, accomplished by use of a heat cradle over the body, constant values for blood flow in the arms were obtained on three different days in one of the patients and the digital pulse amplitude remained approximately twice as great on the right side. When the mean pressures in the radial vessels, as measured on one day, were compared with the blood flows on another day, a correlation was apparent. In the first case the mean pressures in the right and left radial artery were 95 and 80 mm. Hg, respectively, the right-to-left ratio being 1.19. The average arm blood flows were 7.7 and 6.3 cc. per 100 cc. of tissue, with the right-to-left ratio being 1.22. In the second case, the mean pressures in the right and left radial arteries were 121 and 67 mm. Hg, the right-to-left ratio being 1.80. Values for the arm blood flow were 9.9 and 6.9 cc. per 100 cc. of tissue, the right-to-left ratio being 1.43. In the second patient, 400 mg. of tetra-ethyl-ammonium chloride caused decreases in total flows in both arms and the ratio of the flows to increase to 1.84.

The investigations indicate that the blood flow in the arms may correlate with the mean pressure and that under the conditions described the peripheral resistance does not vary significantly between two arms in a patient who has coarctation of the aorta situated proximal to the origin of the left subclavian artery.

PRESSOR AND DEPRESSOR RESPONSES TO TILTING IN NORMAL AND HYPERTENSIVE SUBJECTS. *R. S. Green, M.D. and Arnold Iglauer, M.D. (by invitation) Cincinnati, O.*

In previous studies we have demonstrated that tilting produced mechanical alterations of blood pressure within the aorta due to gravity. At the level of the aortic arch the blood pressure rose during a tilt to a head down position and fell during the return tilt in all subjects studied. These alterations acted as stimuli to large artery proprioceptors.

In normal subjects the elevation of the head down tilt was followed by depressor responses; the fall of the erect tilt by pressor responses, whereby pressure was reflexly returned to approximately the same level within eight to eighteen seconds regardless of position.

Patients with hypertension usually showed striking variation from this normal reflex reaction. Several different patterns of response have been observed and correlated with the clinical status of the patient. Patients with humoral hypertension apparently have delayed or absent pressor and depressor responses. Certain patients have absent depressor activity with normal pressor reflexes suggesting inactivity of 'buffer nerve' function. Others have normal depressor activity with increased pressor response probably due to increased sympathetic tonus.

We believe this method will prove valuable both in studying fundamental reflex mechanisms in hypertension and in evaluating the disease in a given patient.

TREATMENT OF UREMIA BY DIALYSIS ACROSS THE INTESTINAL MUCOSA. *Maurice H.*

Wald, M.D. and Robert A. Reid, M.D. Winnetka, Ill.

The effects of dialysis across the intestinal mucosa by lavage were studied in two cases of chronic terminal uremia. The first case was one of congenital polycystic kidney studied for two months. The other, of advanced nephrosclerosis in a woman whose right kidney had been removed surgically years ago, was studied for one month. By fastening a small bored tube 4 feet from the tip of a Miller-Abbott tube, inflow of dialysing fluid occurs through the former and outflow through the latter which can be allowed to remain at the ileocecal level. The irrigating solution is lactate-Ringer's with added dextrose 5 to 10 per cent. Large quantities of nitrogenous products are abstracted from the blood with lowering of NPN and BUN. A large inflow (priming) is required in intestinal dialysis before outflow effectively equals inflow. Irrigation of the lower ileum and colon is equally efficient and allows for control of edema. Alteration of irrigating solution concentration of glucose controls edema during irrigation. Glucose is absorbed during dialysis necessitating concentrations up to 10 per cent in the irrigating fluid to maintain isotonicity. Sodium chloride in 0.6 per cent concentration is absorbed at all levels in the intestine but sodium chloride deficient solutions will abstract as much as 0.5 mg. per liter. In view of this an irrigating solution containing 0.45 per cent sodium chloride would seem more suitable. Sodium lactate in the dialysing fluid to combat acidosis, hemoconcentration or dilatation during dialysis did not influence blood nitrogen levels.

EFFECTIVENESS OF ENTEROGASTRONE IN MANN-WILLIAMSON DOGS. *H. M. Pollard, M.D., Arnold Wollum, M.D. (by invitation) and Audrey Green, B.S. (by invitation), Ann Arbor, Mich.*

This study was undertaken to determine the effectiveness of oral and parenteral administration of enterogastrone in Mann-Williamson dogs. Medication was carried out prior to and following the surgical procedure. Varying doses of enterogastrone were also used.

All dogs were maintained on a standard diet during the course of study. A group of fifteen dogs in the control group lived an average of eighty-one days following the Mann-Williamson procedure, cause of death being hemorrhage or perforation of the jejunal ulcer. In the group of six animals receiving oral medication (8 gm. per day) the animals when treated three months preoperatively lived an average of 108 days. For the seven dogs receiving enterogastrone for three months postoperatively, ninety-eight days was the average length of life following operation. A series of three animals receiving enterogastrone three months prior to surgery and from ten to fifty-three days following lived an average of 105 days. Three animals receiving 16 gm. enterogastrone per day for sixty days lived seventy-four days.

A group of fifteen animals received 200 mg. enterogastrone subcutaneously following the Mann-Williamson procedure; the average survival time for them was eighty-two days.

EFFECTIVE METHOD FOR THE PREVENTION OF RHEUMATIC FEVER AFTER THE DEVELOPMENT OF STREPTOCOCCAL INFECTION. *W. R. Brink, M.D. (by invitation), C. H. Rammelkamp, M.D., L. W. Wannamaker, M.D. (by invitation), F. W. Denny, M.D. (by invitation) and E. A. Custer, M.D. (by invitation) Cleveland, O.*

From January through June, 1949, at Fort Francis E. Warren, Wyoming, over 1,650 consecutive cases of exudative pharyngitis and/or tonsillitis were observed. These cases were divided into a control and treated group of approximately the same size according to air force serial number. Treatment consisted of the parenteral administration of crystalline procaine penicillin G (suspended in peanut oil containing 2 per cent aluminum monostearate) in doses of 300,000 units on admission and again in seventy-two hours. Later the dosage was changed to 300,000 units on admission, 300,000 units at forty-eight hours and 600,000 units at ninety-six hours. Studies for the detection of rheumatic fever were performed between the third and fourth week following the initial infection. Throat cultures and blood specimens were obtained from all patients on admission and at the time of re-examination.

That these infections were almost exclusively streptococcal in origin was established by the presence of group A streptococci in approximately 80 per cent of all the original throat cultures and a diagnostic increase of the antistreptolysin "O" titer in the convalescent blood of about 80 per cent of the control group.

Of the entire group symptoms suggestive of acute rheumatic fever developed in twenty-seven patients ten to thirty-five days following their initial streptococcal infection; a diagnosis

of definite acute rheumatic fever was made in nineteen cases, seventeen in the control group and two in the treated group. A diagnosis of possible acute rheumatic fever was made in eight cases, six in the control group and two in the treated.

It is concluded that the adequate early treatment of streptococcal infections with penicillin will prevent rheumatic fever in the majority of cases.

RESTORATION OF LOW BLOOD SODIUM AND CHLORIDE LEVELS WITH ISOTONIC AND HYPOTONIC SOLUTIONS BY VEIN. *W. W. Hurst, M.D. and F. R. Schemm, M.D. Great Falls, Mont.*

In our experience best clinical results have been obtained by providing required amounts of electrolyte with proportionately larger amounts of plain water. We have not been able to obtain evidence that a low serum sodium alone indicates a state of dilution of the extracellular fluid. Our data suggest that low levels of sodium and/or chloride usually exist with an actual concentration of the extracellular fluid as well as with a loss in total volume of the extracellular fluid.

Water and electrolyte balance data from two patients treated with our usual clinical technic are reported. When treatment was started both were comatose, markedly oliguric and azotemic. In the first instance in a three and a half day period 20.5 L. of intravenous fluids were given, containing 47 gm. of sodium chloride and 27 gm. of ammonium chloride, representing the equivalent of 9 L. of isotonic electrolyte plus 10.5 L. of plain water. In the second instance in a four-day period 26 L. were given containing 79 gm. of sodium chloride and 18 gm. of ammonium chloride, representing the equivalent of 10 L. of isotonic electrolyte plus 16 L. of plain water. In both instances the sodium-laden solutions as given were one-half isotonic strength except for 3 L. which were isotonic.

In the two cases the serum sodiums rose, respectively, from 120 and 122 to 144 and 138 mEq./L., the plasma chlorides from 280 and 297 to 503 and 528 mg. per cent, the carbon dioxide combining powers fell from 104 and 77 to 82 and 65 volume per cent, the blood urea nitrogen fell from 130 and 100 to 9 and 14 mg. per cent and the serum specific gravities fell from 1.0280 and 1.0297 to 1.0233 and 1.0214. The lower specific gravities appeared optimal and were maintained during convalescence. In both a large positive balance of sodium was maintained by the kidneys in spite of the high water intake by vein and a urine water output of from 3,000 to 5,000 cc. daily.

NEEDLE BIOPSY IN HEPATIC CIRRHOSIS. *J. R. Berman, M.D., Herman Ulevitch, M.D. (by invitation), Leon Schiff, M.D. (by invitation), Ernest Abernathy, M.D. (by invitation) and Edward A. Gall, M.D. (by invitation) Cincinnati, O.*

Seventy-nine needle biopsies of the liver were performed in seventy-eight patients with cirrhosis of the liver. The biopsies were classified as nutritional, postnecrotic and portal cirrhosis. The relative activity and severity of the process in each instance were graded slight, moderate and severe. These interpretations were then compared with the commonly used liver function tests (thymol turbidity, cephalin-cholesterol flocculation, bromsulfalein retention, serum bilirubin and the alkaline phosphatase tests) and with the clinical condition of the patient, i.e., whether hepatic insufficiency was present or absent.

The bromsulfalein retention test proved to be most helpful in assessing the extent of liver damage. In 88 per cent of the instances in which this test was applicable it was significantly elevated. A correlation was also seen to exist between the per cent of dye retained and the severity of the hepatic lesion. This correlation did not apply in the case of the other function tests.

The clinical condition of the patient at the time of needle biopsy was compared with the activity and severity of the cirrhosis. It was seen that the majority of patients with hepatic insufficiency showed a severe lesion. This was most apparent in those cases of nutritional cirrhosis. However, the activity of the lesion did not bear a direct relationship to the presence or absence of hepatic insufficiency.

While the bromsulfalein retention test was the most useful laboratory aid in assessing the severity of the cirrhosis none of the liver function tests provided a reliable index of its activity. Although the majority of patients with hepatic insufficiency showed severe cirrhosis on needle biopsy of the liver, the clinical condition did not adequately reflect the activity of the process. Needle biopsy of the liver provided the only adequate method of evaluating both the activity and the severity of cirrhosis of the liver.

ACUTE INFECTIOUS LYMPHOCYTOSIS. *John B. Moyer, M.D. and George S. Fisher, M.D. Eloise, Mich.*

This is a study of five cases of acute infectious lymphocytosis which occurred simultaneously in sibling children. Since the first description of the disease in 1941 there has been adequate confirmation with additional features being pointed out from time to time. Very briefly, the disease is relatively mild, variably symptomatic or asymptomatic and consistently associated with high leukocyte counts and marked lymphocytosis. Leukocyte counts as high as 147,000 cells per cu. mm. with up to 97 per cent lymphocytes have been observed. Abnormal physical findings are minimal as a rule. The heterophile agglutination remains negative. The principal diseases to be considered in the differential diagnosis are infectious mononucleosis, pertussis and particularly the lymphatic leukemias.

The cases presented here were studied with particular emphasis on lymphocyte morphology and duration of the frequently associated eosinophilia. The usual description of the lymphocyte found in the disease has been "small and mature." Atypical features presented by some of the lymphocytes are discussed. The cases were followed as long as nine months revealing that eosinophilia may persist that long after the onset.

METABOLIC STUDIES OF DEMYELINATING DISEASES: I. BLOOD GLUCOSE, LACTATE AND PYRUVATE IN MULTIPLE SCLEROSIS. *H. Jones, M.D., H. Jones, Jr., M.D., Leitha Bunch, M.D. (all by invitation) and (introduced by) F. D. Murphy, M.D. Kansas City, Mo.*

Blood glucose, lactate and pyruvate concentrations were studied in fifty patients with multiple sclerosis and forty control subjects. Of the fifty patients with multiple sclerosis twenty were in an active phase and thirty in a phase of remission. Control subjects were selected to parallel the age and sex distribution of the patient group. Inquiry eliminated persons with unusually high or low carbohydrate intake during the week preceding the study.

Blood glucose, lactate and pyruvate concentrations were determined by the methods of Folin-Wu (1929), Mendel and Goldscheider (1928), and Bueding and Wortis (1940), respectively. Blood was obtained after a twelve hour fast and at five hourly intervals following the ingestion of 1.0 gm. of glucose per kilogram of body weight.

The average blood glucose curve of the patient group was usual in pattern paralleling that of the control group but elevated above it by +12 to +40 mg. per cent (average +26 mg. per cent). The twenty patients with clinically active multiple sclerosis showed an even greater elevation over the control group, +15 to +55 mg. per cent (average +29 mg. per cent).

The lactate-pyruvate studies revealed a striking dislocation of the pyruvate/lactate ratio in the patient group. The average pyruvate/lactate ratios are as follows, namely, control group, 0.094, fifty patient multiple sclerosis group, 0.121 and twenty patient clinically active multiple sclerosis group, 0.135. The blood lactate level did not vary significantly from the control to the patient groups. The variations of pyruvate/lactate ratio were due solely to elevated blood pyruvate levels. None of the factors known to influence the pyruvate/lactate ratio explained the aforementioned aberration.

FAT AND CELL CONTENT OF BONE MARROW IN HYPER- AND HYPOTHYROIDISM. *A. R. Axelrod, M.D. and Lawrence Berman, M.D. (by invitation) Detroit, Mich.*

It is generally assumed that a relationship exists between the structure of bone marrow and activity of the thyroid gland. The widely quoted concept of hyperplasia of bone marrow in hyperthyroidism and hypoplasia in hypothyroidism is based on reports of only nineteen patients in whom fat and cell content of aspirated marrow were analyzed by volumetric methods which we have previously shown to yield unreliable results.

We present a study of twenty-seven patients with hyperthyroidism and nine patients with hypothyroidism based on quantitative analysis of fat and cell content of histologic sections of sternal marrow obtained during life. Fat content was decreased and the cellularity increased in 74 per cent of the patients with hyperthyroidism. In hypothyroidism the fat content of the marrow was normal but the cell content was very low in three cases (less than 2 per cent). In these three patients the bulk of the marrow space was occupied by hyperemic and acellular tissue.

Although sternal marrow hyperplasia is usual, it is not a constant finding in hyperthyroidism. We cannot support the claim that sternal marrow is usually excessively fatty in hypothyroidism. However, it may be hypocellular.

Although increased cellularity of the sternal marrow in hyperthyroidism is not a constant

finding, it is to be noted that postmortem studies show extension of the marrow organ. Likewise, there is a decrease of total active marrow in hypothyroidism. Hence, despite normal findings in the sternum the marrow organ may be hypertrophied in hyperthyroidism and atrophied in hypothyroidism.

EVALUATION OF HYPOSPRAY (JET INJECTION) TECHNIC FOR ADMINISTRATION OF INSULIN. *G. M. Todd, M.D., F. S. Perkin, M.D., T. M. Brown, M.D. (all by invitation) and (introduced by) Gordon B. Myers, M.D. Detroit, Mich.*

Hypospray, a new mechanical device for jet injection of solutions or fluid suspensions without a needle, was used for administration of protamine zinc insulin and modified PZI, type NPH 50. Calibration of the instrument for measurement of dosage apparently is highly accurate and depth of injection can be controlled. The efficacy of Hypospray was compared with that of syringe injection in twenty hospitalized diabetics, all but four of whom required 40 to 80 units daily. Response to insulin administered by syringe was observed for three to fifteen days. Hypospray injections were then given for three to ten days using the same dose and type of insulin as in the control period. A few patients were observed during a second period of syringe injections. Blood sugar time curves and fractional urinalyses were compared for both methods of injection.

The degree of control of hyperglycemia and of glycosuria obtained by Hypospray injection was comparable to that by syringe. No consistent or significant alteration of the speed, intensity or duration of action of the insulin was observed. No unusual or severe cutaneous reactions were observed even after repeated injections at one site. Mishandling of the instrument with loss of insulin during injection was rare as experience increased.

Patient preference for Hypospray injections was virtually universal, as pain usually was briefer and less intense than with the needle. Hypospray has been used successfully at home both by juvenile and adult diabetics.

RECURRENCE VERSUS REINFECTION IN AMEBIASIS. *W. H. Shlaes, M.D., F. R. Steigman, M.D., A. Stein, M.D., V. M. Young, M.D. (all by invitation) and O. Felsenfeld, M.D. Chicago, Ill.*

Because many adequately treated cases of chronic intestinal amebiasis frequently show relapses it was decided to investigate the possibility of the patients becoming reinfected in their own households by asymptomatic or relatively symptomless undiscovered cases of amebiasis. All members of the families of 135 patients with amebiasis were examined. The size of these families varied from two to ten persons. In 88.9 per cent of the families at least one, in 66.7 per cent two or more and in 7.5 per cent all members of the family harbored E. histolytica.

It is believed that these findings bring up the question as to whether treated patients in whom symptoms suddenly develop again are not victims of family reinfection rather than relapses. Thus a re-evaluation of the general management of amebiasis becomes imperative.

BAL AND TESTOSTERONE PROPIONATE IN THE TREATMENT OF MERCURIC CHLORIDE POISONING. *R. P. Levy, M.D., T. W. Moir, M.D. (by invitation) and Max Miller, M.D. Cleveland, O.*

Because BAL (2,3 dimercaptopropanol) has been shown to be an effective antidote for only limited doses of mercuric chloride, the treatment of mercury poisoning remains a problem. Testosterone, possessing a trophic action on renal tubules, has been reported an effective agent in the therapy of experimental mercury poisoning when given before or after the poison. In this investigation the effectiveness of testosterone in HgCl poisoning was re-evaluated and its value when used together with BAL was determined.

Albino male rats of a homogeneous strain were used and a dose of mercuric chloride

Treatment	No. of Animals	No. Dead	Mortality (Per Cent)
Control	27	15	56
BAL alone	16	3	19
Testosterone 0.1 mg. per day	10	4	40
BAL and testosterone 0.1 mg. per day	10	1	10
Testosterone 1.0 mg per day	10	4	40
BAL and testosterone 1.0 mg. per day	10	0	0
Testosterone 10.0 mg. per day	10	4	40
BAL and testosterone 10.0 mg. per day	10	1	10
Testosterone 25.0 mg. per day	27	20	74
BAL and testosterone 25.0 mg. per day	27	4	15

selected (6 mg./kg.) that was approximately LD_{50} for control animals. Beginning thirty minutes after poisoning, treatment was begun with graded doses of testosterone propionate, alone and in combination with BAL, 30 mg./k. initially and smaller doses daily for eight days. The data were as shown in the Table on page 814.

Statistically, these data show that testosterone in doses as high as 25 mg. daily is ineffective against mercuric chloride. The therapeutic value of BAL is demonstrated by the reduction in mortality from 47 per cent of fifty-seven control animals to 9 per cent of fifty-six treated. The addition of testosterone to BAL treated animals did not significantly improve the survival rate. Thus this experiment confirms the protective effect of BAL under the circumstances given, while testosterone either alone or in combination with BAL seemed without therapeutic effect.

LIMITATIONS OF THE USE OF LUMBAR SYMPATHECTOMY IN ISCHEMIC DISEASES OF THE LOWER EXTREMITY DUE TO ARTERIOSCLEROSIS. *R. Glenn Smith, M.D. and D. A. Campbell, M.D. Eloise, Mich.*

It is generally accepted that lumbar sympathectomy plays a major role in the treatment of ischemia of the lower extremity due to vasospastic diseases. Recent reports indicate that there is increasing interest in applying this form of therapy to the treatment of ischemia due to arteriosclerosis. Observations in a series of 100 consecutive cases of arteriosclerotic disease of the lower extremity treated with lumbar sympathectomy permit certain conclusions in respect to indications and early results.

In the less advanced cases relief of pain and coldness and an increase in exercise tolerance were benefits almost uniformly obtained although in some cases sustained for only short periods. Poor results included late cases that exhibited extensive gangrene as well as those with a high degree of occlusion as demonstrated by arteriography.

Our observations suggest that lumbar sympathectomy offers little if (1) extremities have frank gangrene and occlusion of the arterial tree at or above the bifurcation of the popliteal artery, (2) extremities demonstrate a fall in skin temperature in response to lumbar sympathetic block and (3) extremities exhibit a combination of signs and symptoms which include an antecedent history of intermittent claudication, arterial occlusion, marked edema and severe resting pain. Inevitably, gangrenous digits or feet requiring major amputation developed in such patients who appeared to be completely uninfluenced by sympathectomy.

Case Reports

Clinical Aspects of Ochronosis*

With Report of a Case

EUGENE L. COODLEY, M.D. *and* ANTHONY J. GRECO, M.D.
Los Angeles, California

A REVIEW of the literature on ochronosis indicates that this disease is quite rare. In 1916 Oppenheimer and Kline[1] presented a case before the New York Academy of Medicine as a diagnostic problem. It evidently remained a baffling problem because it was not until 1922 that they published a report of their case and gave a complete survey of the world literature on ochronosis up to that time. The next exhaustive paper in the American literature on ochronosis was by Smith[2] in which he thoroughly studied and described the ocular manifestations of this disease and showed that many cases present only the ocular pigmentation and occasionally no alkaptonuria. Since both of these papers omitted some points in the evolution of our knowledge of the subject and because other writers have stressed a particular manifestation of this disease, there exists today some confusion regarding the total picture of this disease entity.

Our first objective in this paper will be to correlate the primary manifestations of ochronosis, i. e., alkaptonuria, pigmentation and arthritis, and to present a clearer concept of the development of our knowledge about this perplexing disease. Our second objective will be to stress the diagnostic features of this disease and to emphasize the more important conditions from which it must be differentiated. It is not generally realized that ochronosis in its early stages may show only scattered pigmentation in selective areas and minimal arthritis so that other diseases having pigmentation as a leading component must be considered in diagnosis.

We have derived much of the historical data of our paper from the complete reviews of Oppenheimer and Kline[1] and of Smith[2] but in addition have attempted to review the various contributions in chronologic sequence. In 1823 Marcet described a substance found in urine which caused a grey-black pigmentation of linen. Virchow in 1866 recorded the first case of this disease. His patient had died of a crushing injury and the autopsy revealed pigmentation of the eyes, of the skin over the bony prominences, of the hands and feet, and of the cartilages of the ribs and large joints. He also described pigmentation of the intima of the large vessels, of the bronchial cartilages and of the dura. He found that the pigment was deposited as small grains of an ochre-colored substance in the tissues. In 1858 Boedeker found in a glycosuric patient a second reducing substance which was not sugar but reacted with alkali to form a black color immediately and he called this "alkapton body." In 1887 Marshall found that the alkapton body was what he called glycosuric acid. Later Wolkow and Bauman named it "homogentisic acid" because it is a homologue of gentisic acid. They also showed that the behavior of alkapton urine is due to this acid. In 1892 Hanseman

* From the Medical and Dermatology Service, Wadsworth Hospital, Veterans Administration Center and the Department of Medicine, University of California, Los Angeles, Calif. Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

reported a case of ochronosis without alkaptonuria and without melanuria.

In 1902 Albrecht and Zdareck first suggested that alkaptonuria is the cause of ochronosis. In 1899 ocular ochronosis first appeared in an American textbook on ophthalmology by Hecker and Wolf. Osler[1] observed it in a brother of Marchall's first alkaptonuric patient and in 1904 described this case in detail emphasizing the pigmentation of the ears and eyes, the peculiar gait and stance, and the severe arthritis.

Pick in 1904 reported the first case of ochronosis which followed prolonged application of phenol to a leg ulcer and after thorough chemical studies concluded that ochronosis is of three different varieties: First, the *endogenous group:* (1) aromatic substances in the blood are acted upon by an enzyme with the production of alkaptonuria; (2) homogentisic acid and tyrosin in the blood are acted upon by an enzyme with the production of melanuria; second the *exogenous group:* Hydroquinone and pyrocatechin in the blood are acted upon by an enzyme with the production of melanuria. These concepts have been largely preserved to the present day.

In 1905 Osler saw a case in England which had been reported as Addison's disease in the Lancet; he corrected the diagnosis and this patient was reported as the first British case of ochronosis by Pope in the Lancet in 1906. In 1908 Allard and Cross described the arthritis in more detail. In 1909 Bedard reviewed the literature of ochronosis and concluded that about 20 per cent of the cases he reviewed had shown some disturbance of the cardiovascular system during life. He suggested that these cardiovascular lesions, like the arthritis, were due to the basic metabolic disorder. In 1910 Kolaczek, while operating on an apparently tuberculous fistula of the knee, found black pigmentation in the cartilage of the knee. He investigated this patient's family and found that two sisters had both alkaptonuria and ochronosis—their parents and maternal grandparents were cousins. He also tabulated forty-one cases from the literature, in nineteen of whom an autopsy had been performed. These cases all showed some cardiovascular lesions and sixteen of them also had arthritis of large joints and the spine. He described the cardiovascular lesions as pigmentation of the intima of large vessels and of the endocardium but he did not mention involvement of the myocardium. (Other authors, however, have described myocardial pigmentation).

Poulsen in 1910 reported ten cases in a classical thesis on ochronosis and no more complete description can be found. However, he made no mention of involvement of the myocardium. He stated that "outside of the skeleton, the pigment is deposited as a rule only in the endocardium, intima of larger blood vessels, kidneys, rarely in other places as bits of cartilages in the tonsil, connective tissue of lungs, and thyroid; in perichondrial fat and in dura. It is frequently found in scleras, epidermis, in nails, and prostate." In 1913 Burger and Umber reported a family of eight children of an alkaptonuric father and normal mother; four of the children were alkaptonuric and had severe articular lesions while the remaining four children had no alkaptonuria or arthritis, in fact, were perfectly healthy.

In 1945 Soderbergh[4] reported the roentgenologic features of this disease. He described an ankylosing process of the spine associated with hypertrophic arthritis of the vertebrae, hips and shoulders, with alternating osteoporosis and osteosclerosis. Pomeranz et al.[5] stated that the characteristic roentgenographic findings of alkaptonuric ochronosis were found in the spine, pelvis, shoulder and knee joints. In the spine the most striking feature was the universal calcification of the intervertebral discs, probably secondary to cartilage degeneration. The shoulders showed narrowing of joint space, resorption of humoral heads, calcific deposits in the soft tissues and eburnation of the articular surfaces of the glenoid fossae. Pelvic bones showed narrowing of sacroiliac articulations and soft tissue calcifications. The knees showed calcification within the quadriceps tendons. The

ears showed small calcific deposits within the helix and in the antitragus. The small joints displayed periarticular swellings without calcific depositions. Occasionally small punched out areas in the small joints resembling gout are seen.

In 1922 Oppenheimer and Kline[1] reported their case. It was not until 1916 that Friedenwald and de Schweinitz examined the ocular lesions in Osler's patients and they were the first to prove that the pigment is deposited in the sclerae and not in the conjunctivae; they also observed that the pigment did not extend to the covered portions of the eyeball. In 1926 Sollman made the first slit lamp examination together with a comprehensive study of ocular ochronosis and confirmed the observation that the pigment is deposited in the sclerae at the periphery of the cornea. Smith's[2] complete review of the ocular manifestations appeared in 1942. In 1944 Young[6] reported a case of occult ochronosis which was discovered during prostatectomy when black calculi were found in the prostate. Young stated that five other cases with calculi had been described but only one during life; he stated that a number of cases with renal calculi had been described. In 1945 Ekelund[7] reported two cases of ochronosis but did not describe any new findings. In 1946 Boads[8] reviewed again the pigmentary alterations in ocular ochronosis.

REPORT OF NEW CASE

This fifty-four year old white male was admitted to the hospital on December 9, 1946, with a history of sudden onset of severe dyspnea the day before entry, but no pain, nausea, vomiting or perspiration. For the past two years he had had moderate exertional dyspnea with frequent ankle edema in the late afternoons but no nocturnal asthma, chest pain, known arrhythmias, dizzy spells, headaches or syncope. There was no history of rheumatic fever, syphilis, goiter, anemia or congenital heart disease. He was told that he had high blood pressure four years before but had had no treatment. At the time of entry he had been very dyspneic and orthopneic for two days.

He gave a history of a greyish black discoloration of the skin which came on during a period of one year in 1919 and had remained unchanged since. There was no preceding illness, no local skin disease, no history of injections, no use of silver or antipyrine drugs, no history of cyanosis, no symptoms or signs of porphyria and no use of phenol drugs. There was no history of any other pigmentary disease such as melanosis. His urine had been the color of beer since 1919. He had also noted the staining of his clothing and linen, not removable by soap or water. He stated that the discoloration appeared to lighten or darken slightly, depending upon his diet or state of mental well being.

Four years before entry he developed an almond-shaped, firm swelling of the palms and proximal interphalangeal joints, and also chronic pain in the low back region. The joint symptoms were not accompanied by fever, chills, redness, heat or weight loss. The family history was entirely negative for any type of pigmentary disease or urinary abnormalities.

The patient was well developed and fairly well nourished. His skin showed a diffuse grayish black discoloration which was most marked on the cheekbones, ears and carpal joints; and he was moderately orthopneic and slightly cyanotic sitting up in bed. The pigmentation was almost black in color over the zygomatic bones, in the upper cartilage of the ears, lateral portions of both sclerae and on the palmar and dorsal aspects of both hands. The pigmentation was more diffuse and of a lighter hue over the chest, abdomen and extremities, becoming lighter peripherally. The skin of the extremities showed a dry, scaly appearance. The mucous membranes of the mouth were not pigmented except for a few dark spots on the upper gingiva. Ear, nose and throat examination was normal otherwise. There was no enlargement of the thyroid nor any adenopathy.

The chest was symmetrical and showed almost normal expansion but the respirations were of a rapid, shallow, wheezing type. Both lung bases had coarse, moist, crepitant rales with many rhonchi heard in the mid-lung fields. There were no marked changes in voice sounds or percussion nor any evidence of fluid. The heart was enlarged to the left on percussion with the point of maximum impulse in the sixth interspace 3 cm. to the left of the mid-clavicular line. The rate was 100 with regular sinus rhythm. There was a loud, blowing grade III systolic murmur in the third left interspace,

transmitted throughout the chest with a harsh grade II systolic murmur heard in the aortic area. The second sound was not heard. Blood pressure was 110/90.

The liver was enlarged 2 fingerbreadths below the right costal margin and was moderately tender. The abdomen was normal otherwise; the back was normal and the genitalia were normal except for pigmentation of the scrotal sac. The extremities revealed minimal cyanosis, no edema and no clubbing. The vessels were moderately sclerotic and the peripheral pulses were poorly felt. The joints showed a diffuse firm swelling, chronic in type, involving the proximal interphalangeal joints and the first and second carpal joints with marked limitation of motion; no bony spurs were noted. The knees likewise showed a diffuse, non-tender, chronic swelling with a firm calcified prominence in the right popliteal region. There was no other joint involvement grossly. The spine had some limitation of forward and backward bending.

Laboratory studies revealed the following: Temperature 97°F., pulse 110, respiration 25. His red blood count was 3.44 million; hemoglobin 63 per cent of 15.7 gm.; white blood count 16,800 with a differential of 85 polymorphonuclears, 9 per cent lymphs and 5 per cent monocytes. Sedimentation rate was 28 mm./hr. Entry urinalysis showed 2 plus albumin, negative sugar, and a few white blood cells on microscopic examination; subsequent urines were practically unchanged. Electrocardiogram on entry showed diphasic Rs in Leads I and II and small R in CF1, CF2, and CF3, depressed S-T segments in Leads I and II, elevated and bowed S-T segments in CF1, CF2, CF3 and CF4, and depressed S-T in CF5 and CF6. The tracing was read as indicating myocardial infarction, anterolateral wall. A subsequent tracing three days later showed diphasic T in Leads I, CF2, CF3, CF4, CF5 and CF6 with an absent R wave in CF1, CF2 and CF3, and elevation of S-T in CF1 and CF2. This tracing was believed to represent a recent anterior wall myocardial infarct.

Other laboratory studies showed the following: blood phosphorus was 4.2 mg./100 cc., blood calcium was 7.9 mg./100 cc.; icteric index was 15 units; and bilirubin 0.7 mg. bilirubin/100 cc. five days after entry. The Wassermann reaction was negative on two occasions; sedimentation rates remained elevated but the white blood count returned to 8,800 after one week; repeated urines were positive for alkapton bodies and melanin, negative for porphyrins and urobilinogen. His urines, which were dark on voiding, turned black on alkalinization or exposure to air for several days (oxidation). (Fig. 1.)

The patient ran a rather stormy eight- or nine-day course in the hospital before death

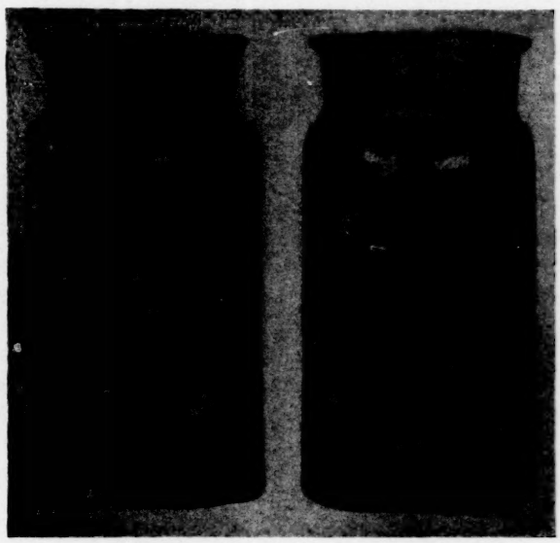


FIG. 1. No. 1 urine immediately after addition of alkali; No. 2 urine after exposure to light for twenty-four hours.

ensued. He was treated with oxygen, intravenous aminophylline, opiates and other sedatives, and diuretics including ammonium chloride and mercurials. He was also begun on dicumarol® 300 mg. the first day, 200 mg. the second day and 100 mg. daily thereafter dependent on the prothrombin time. He remained very weak and was able to take only small amounts of food or liquid by mouth. The dyspnea gradually improved and the liver was no longer palpable after five days in the hospital. He began vomiting after five days and continued to do this several times daily until his death. The pulse remained around 100, regular, and his blood pressure persisted at 103–115/80–90. He was given intravenous glucose in water twice daily. He gradually sank into a stupor and became increasingly weak. The day before death he was quite cyanotic. There was no ankle or liver edema and only occasional basal lung rales bilaterally. Pulse was 110 but regular. He became more stuporous and expired on December 19, 1946.

At autopsy, the patient exhibited very marked generalized atherosclerosis of the aorta and its major branches. The coronary arteries also

exhibited this severe atherosclerosis. The intimal surfaces of the aorta and all of the major artery branches were slated grey, blue in color. Deeper black pigmentation occurred at the sites of atherosclerotic plaques. In the heart the sites of recent and old myocardial infarction were pigmented bluish black. Foci of encephalomalacia, the result of severe cerebral atherosclerosis, were also pigmented bluish black.

The ochronotic pigmentation involved all of the skin surfaces and conjunctivae. There was pigmentation in all the cartilages, elastic, hyalin and fibrocartilage. Shades of blue or bluish black were found in the fascial planes of the body, in the tendons, ligaments, perichondrium, periosteum, dura and beneath the serosal surfaces of the body. Bluish black fluid was found in the larger joint spaces of the body. Secondary to this cartilaginous pigmentation, degenerative changes were found in joints but the laryngeal and bronchial cartilages showed no degenerative changes. A crumbling, fragmenting, degenerative process resulted in destruction of the articular surfaces, and in such joints as the intervertebral disc, symphysis pubis and the joint between the body and manubrium of the sternum. Collapse of the intervertebral discs had occurred in varying degree with osseous union between several of the vertebral bodies. Ochronotic pigmentation was found in the convoluted tubules of the kidney, and was also observed in the calculi of the prostate and seminal vesicles.

Final anatomic diagnosis: (1) Generalized atherosclerotic disease with recent and old coronary thrombosis and myocardial infaction; (2) ochronosis with pigmentation of skin, cartilages, tendons, fascia, ligaments, periosteum, kidney tubules, prostatic and seminal vesicle calculi. Ochronotic osteoarthritis of joints.*

COMMENTS

Nothing was known about the etiology of this condition until Osler found ochronosis in Marshall's alkaptonuric patient and he was the first to suggest that the two conditions were related. Garrod[9] cited many alkaptonuric families with consanguinity and stated that the similarity of occurrence of alkaptonuria and albinism suggests that the manifestations of the two conditions are governed by the same laws—both are apt to occur in brothers and sisters from parents who do not exhibit the anomaly, and direct transmission from parent to child is rare. He stated that 38 per cent of the siblings of consanguineous cousins had albinism and 29 per cent of the alkaptonuric patients were siblings of cousins. Cases in families have been reported in which the parents were cousins and occasionally in which the maternal grandparents were cousins. Alkaptonuria is an example of recessive inheritance although one family reported exhibiting dominant transmission. The recessive inheritance of abnormal traits may be thought of as inheritance from both parents as contrasted with inheritance from one parent only in the case of dominant abnormalities.

The disease occurs about equally in both sexes, being slightly more frequent in males; it has been reported only in the white race. Age apparently plays no role and the disease has been reported among children as well as older people.

Urine Characteristics. The urine is dark amber when passed but on standing rapidly becomes darker. In twenty-four hours it became black in our case. The urine tends to stain linen dark grayish black and this stain deepens on attempting to wash it off with soap and water. Garrod[9a] listed the following tests to detect homogentisic acid in the urine: (1) exposure to air turns the urine brown or black; (2) addition of alkali produces a similar effect; (3) reduction of copper solutions; (4) non-reduction of alkaline bismuth solutions (Nylander's reagent); (5) non-reaction to fermentation tests; (6) non-rotation of polarized light; (7) reduction of silver lactate in the cold; (8) addition of a dilute solution of ferric chloride produces a transitory deep blue color; (9) reduction of silver nitrate in the cold (in the absence of ammonia); (10) addition of a 1 to 10 per cent ferric chloride solution of 5 cc. or urine with a dropper reveals a transitory greenish coloration (additional drops of reagent produce no

* A detailed pathologic analysis of this case will be published at a later date by Dr. Leo Kaplan, of the Dept. of Pathology, General Medical and Surgical Hospital, V.A.C., Los Angeles, Calif.

color changes); (11) production of a yellowish precipitate by Millon's reagent (10 gm. of mercury in 20 gm. of nitric acid).

Janney[9b] has questioned the specificity of some of these tests for detecting homogentisic acid however.

In addition to the above tests we have made a new observation on the behavior of alkaptonuric urine under a Wood filter lamp. We found that the alkaptonuric urine, which had not been alkalinized, produced a dark olive-green fluorescence; the alkalinized alkaptonuric urine fluoresced a bright light green color; normal urine, both alkalinized and non-alkalinized produced no fluorescence and the alkaline solution that was used (15 per cent KOH) produced no fluorescence. We, therefore, conclude that the alkapton body in the non-alkalinized urine was responsible for the deep olive-green fluorescence, and the alkaline alkapton body for the brighter and more intense light green fluorescence.

Differential Diagnosis. If one keeps in mind the characteristic triad of pigmentation, alkaptonuria and arthritis there should be no difficulty in the recognition of this disease. Since, however, the early cases may show only minimal arthritis and ocular signs, the pigmentation may prove to be an essential feature in diagnosis, so we must differentiate other diseases characterized by pigmentation, such as hemochromatosis, Addison's disease, arsenical poisoning, argyrosis, porphyrinuria.

Another condition which may closely simulate the pigmentation of ochronosis is the pigmentation associated with the use of atabrine. Sugar and Waddell,[10] Schechter and Taylor[11] and Jeghers[12] have all discussed the production of pigmentation by the prolonged administration of atabrine. Sugar and Waddell[10] have reported ten cases of pigmentation of the hard palate, nail beds, nasal cartilage, cartilage of the ears, epiglottis and trachea, skin conjunctivae and corneoscleral limbus following the prolonged use of atabrine. No arthritis or urinary abnormalities were noted. The condition lasts six to eight months and spontaneously regresses on cessation of therapy.

Therapy. Treatment has been aimed at correction of the metabolic disturbance, limiting particularly the proteins and feeding a diet high in carbohydrates. Gibson and Howard[13] have pointed out that when humans were put on a diet low in vitamin C and fed tyrosine, homogentisic acid was produced in the urine; the addition of vitamin C to the diet abolished the homogentisic acid from the urine. However, vitamin C was ineffectual in the therapy of a case. Likewise, the administration of crude liver intramuscularly experimentally abolished homogentisic acid from the urine for a period of eight to ten hours and the use of this substance has also been attempted in therapy. If the condition is the result of the prolonged use of some phenolic compound, such as is commonly seen in the treatment of chronic skin diseases, the clinical manifestations will be improved upon the discontinuance of the use of these substances.

SUMMARY

1. A review of the literature on ochronosis has been presented emphasizing the evolution of knowledge about this disease.

2. Alkaptonuria may be considered an inborn error of protein metabolism resulting in the excretion of a substance known as homogentisic acid in the urine; this substance probably represents an intermediate product of the normal metabolism of certain amino acids. The condition may also be the result of prolonged exposure to phenolic compounds. Ochronosis is the clinical state of pigmentation by the alkapton compounds with particular localization in the cartilaginous structures and the cardiovascular system.

3. The differential diagnosis of other diseases showing pigmentation has been stressed in detail, and the particular diagnostic features of ochronosis have been emphasized. A new observation on the fluorescent behavior of urine containing alkapton bodies has been made.

4. The case history of a patient with alkaptonuria and ochronosis has been presented.

REFERENCES

1. Oppenheimer, B. S. and Kline, B. S. Ochronosis. *Arch. Int. Med.*, 29: 732, 1922.
2. Smith, J. W. Ocular manifestations of ochronosis. *J. A. M. A.*, 120: 1282, 1942.
3. Osler, W. Ochronosis, the pigmentation of cartilages, sclerae and skin in alkaptonuria. *Lancet*, 1: 10, 1904.
4. Soderbergh. Roentgen features of ochronosis. *Nord. med. Ark.*, 48: 4, 1915.
5. Pomeranz, M. M., Friedman, L. J. and Tunick, I. S. Roentgen findings in alkaptonuria, ochronosis. *Radiology*, 37: 295–303, 1941.
6. Young, H. H. Calculi of prostate associated with ochronosis and alkaptonuria. *J. Urol.*, 51: 48–58, 1944.
7. Ekelund, D. Alkaptonuria and ochronosis; report of two cases. *Nord. med.*, 28: 2421–25, 1945.
8. Boads, L. A. Ocular alkaptonuria-ochronosis pigmentary alterations. *Prensa méd. argent.*, 33: 1390–93, 1946.

9*a*. Garrod, A. E. Inborn Errors of Metabolism. 2nd ed. pp. 43–64. London, 1923. H. Frawds, Hodder, Stoughton.

9*b*. Janney, N. W. Case of ochronosis. *Am. J. M. Sc.*, 156: 59–68, 1918.

10. Sugar, H. S. and Waddell, W. W. Ochronosis-like pigmentation associated with the use of atabrine. *Illinois M. J.*, 89: 234–38, 1946.
11. Schechter, A. J. and Taylor, H. M. Atabrine pigmentation. *Am. J. M. Sc.*, 192: 645, 1936.
12. Jeghers, H. Pigmentation of the skin. *New England J. Med.*, 231: 88, 231: 122, 231: 181, 1944.
13. Gibson, R. B. and Howard, C. P. Ochronosis. *Arch. Int. Med.*, 28: 632, 1921.

Sweat Test Simplified for Clinical Use*

ALAN LESLIE, M.D., *and* MELVIN H. LEVIN, M.D.
Los Angeles, California

SWEAT has been studied by numerous investigators, prominent among whom have been Kuno,[1] Dill,[2] McCance,[3] Keutmann, Bassett and Warren,[4] and Conn and Johnston.[5] Recently, Conn[6] reported that the concentration of sodium and chloride in sweat appears to reflect the desoxy-like corticosteroid activity of the adrenal cortex. The conditions under which sweating occurred or was induced have varied widely in different laboratories, with corresponding differences in volumes and composition of the sweat. The various investigators have employed special apparatus such as thermal rooms and thermal cabinets with carefully controlled temperature and humidity. Furthermore, there has been considerable variation in methods of collection. These collection methods have been tedious and time consuming, although essential to careful metabolic studies. A simple technic for obtaining thermal sweat would extend the availability of this test of adrenal cortical function.

Gibbon and Landis,[7] Pickering,[8] Mendlowitz,[9] and Goetz and Ames[10] in studying peripheral circulation have employed a simple method of body warming to produce relaxation of sympathetic tone. One of the observed phenomena was the appearance of thermal sweat. It was decided to investigate this procedure specifically for sweat production. The following modification of the sweat test was evolved:

The subjects are on average uncontrolled diet and fluid intake. They are tested under fasting conditions between 8:00 and 9:00 A.M., a half hour after drinking 500 cc. of tap water. They are attired in hospital pajamas and have a Turkish towel around the neck. One upper extremity to a point just proximal to the elbow is prepared by gentle scrubbing with white soap and water and then rinsing copiously with tap water followed by distilled water. The arm is

FIG. 1. Method in operation. (Note: If double volume of sweat is desired, gloves may be placed on both arms and an appropriate leg bath used for body warming.)

dried with a towel previously rinsed in distilled water to render it electrolyte-free. It is then encased in an elbow length rubber glove made electrolyte-free by washing with a detergent, rinsing thoroughly with tap and then distilled water. (The gloves, the prepared forearms and the distilled water itself were repeatedly tested for possible electrolyte contamination and found to be electrolyte-free.)*

* We employ a Matex obstetrical glove obtained from the Massilon Rubber Co. This is prepared for use by the following steps: (1) Wash in cold water softened by the addition of Raindrops brand water softener. (Los Angeles water is "hard." A water softener may not be necessary in soft water areas.) The detergent used is Dreft. (2) Rinse thoroughly in three changes of cold tap water. (3) Rinse thoroughly in three changes of distilled water. (4) Dry in air, hanging glove over rack covered with Patapar parchment paper. (5) Turn and allow inside to dry in air. (6) Wrap in Patapar. The operator, prior to preparing the gloves, washes his hands and arms to the elbows according to steps 1 to 3. The basins used

* From the Medical Service, Wadsworth Hospital, Veterans Administration Center, Los Angeles, California. Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions of the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

The subject is seated comfortably. (Fig. 1.) The *unprepared* forearm and lower third of arm are immersed for one hour in a thermostatically controlled water bath maintained between 43°C. and 45°C. Sweat is collected in the glove. The temperature and humidity of the room are not

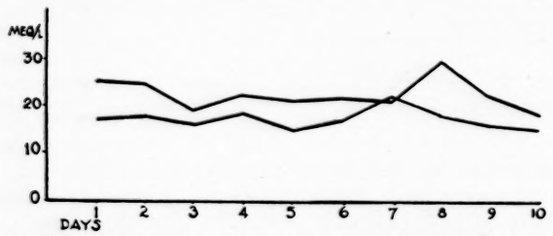


FIG. 2. Sweat sodium in two normal subjects tested on ten consecutive days.

controlled. (Under the experimental circumstances these varied between 25°C. and 28°C. and 45 per cent and 60 per cent, respectively.) At the end of the hour the glove is removed and the accumulated sweat is pipetted into an electrolyte-free test tube. The clear, supernatant fluid is used for the electrolyte determinations after the epithelial debris is removed by gravitation or centrifugation. Although sweat appears in appreciable quantity over the body it was decided, for the sake of simplicity, to collect only the glove sample since, according to Dill, Hall and Edwards,[11] hand sweat has about the same chloride concentration as pooled body sweat. Since the subjects are perfectly comfortable during the testing period, the procedure is applicable to sick patients as well as to normal subjects.

The Beckman flame photometer was used for the sodium determinations.* The chloride determinations were made according to the method of Sendroy[12] as modified by Kingsley and Dowdell.[13]

RESULTS

The volume of sweat samples obtained from twenty-one normal subjects varied between 1.5 and 22.0 cc.† As shown in Table I the sodium concentrations ranged from 15.9 to 55.4 mEq./L.; the proportionately lower chloride levels ranged from 10.9 to 43.5 mEq./L. There was no correlation between volume and electrolyte concentration. These figures for normal subjects are

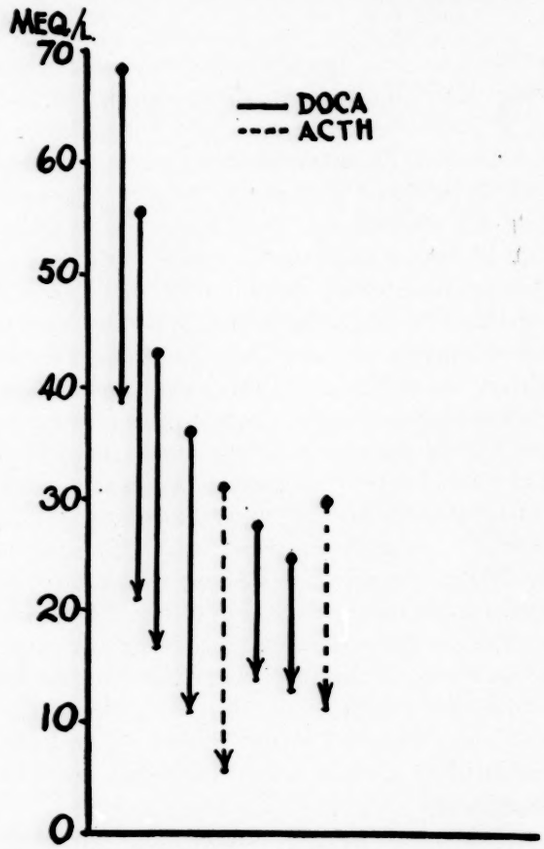


FIG. 3. Effect of DOCA and ACTH on sweat sodium in miscellaneous subjects.

comparable to those reported by Conn.[6] The difference in testing technic may well account for variations. Four normal subjects from the reported group were exposed in a thermal room to a temperature of 44°C.

are prepared similarly. When turning the glove inside out, the operator inserts his forearm full length into the glove which is then peeled off by an assistant. This insures that the collecting surface of the glove is not directly handled.

* We are indebted to Dr. C. Dubbs for these determinations.

† Three patients tested by this method failed to sweat either into the glove or anywhere else on the body. The oral temperature of two of these patients, one with severe postural hypotension, one with advanced Hodgkin's Disease, rose to 101.6°F. and 103.6°F., respectively. In the normal subjects, all of whom perspired, no temperature elevation occurred except for a few isolated instances when a reading of 99°F. was observed. The third patient who did not perspire, a man in congestive heart failure, showed no elevation of temperature at the end of the test period. This suggests that in conditions attended by impaired peripheral circulation there is inadequate return of heated blood to produce body warming. Therefore, this method is presumably not adapted to the study of such conditions.

and a relative humidity of 90 per cent for one hour. Glove sweat, which appeared in large volume, revealed markedly higher electrolyte figures, especially with respect to the chloride concentration.

TABLE 1
RESULTS OF SWEAT TEST IN TWENTY-ONE NORMAL SUBJECTS

Name	Sex	Age	Volume (cc.)	Na (mEq./L.)	Cl (mEq./L.)
I. S.	F	25	3.0	47.2	38.0
J. R.	F	32	6.0	21.5	12.0
M. T.	F	25	2.5	29.6	21.0
B. B.	F	27	1.5	23.1	19.5
M. J.	M	29	6.0	25.4	20.0
P. B.	M	33	7.5	17.7	10.9
R. E.	M	33	3.0	27.2	16.0
W. B.	M	24	3.0	43.5	37.0
M. C.	M	32	5.0	20.2	10.9
M. S.	M	22	22.0	36.3	25.0
R. M.	M	29	7.0	43.9	43.5
J. K.	M	28	2.5	41.3	28.0
J. A.	M	38	1.5	23.0	11.0
M. L.	M	35	5.0	15.9	13.5
A. S.	M	30	15.0	28.0	20.0
R. A.	M	26	5.0	24.2	14.5
W. M.	M	28	18.5	25.0	23.0
E. M.	M	22	5.0	55.4	43.0
W. H.	M	27	15.0	34.8	27.0
M. L.	M	29	4.0	17.3	16.0
A. L.	M	39	4.0	20.7	11.0

Two normal subjects were tested on ten consecutive days. Figure 2 demonstrates that the electrolyte concentration fluctuated within a narrow range. This indicates that repeated testing did not result in acclimatization and suggests, therefore, that single tests are representative.

Figure 3 illustrates the uniformly sharp depression of sodium in sweat obtained by this method following the administration of desoxycorticosterone (DOCA) 10 mg./day or pituitary adrenocorticortrophic hormone (ACTH) 40 mg./day. The chloride depression was roughly parallel to the sodium depression but the reversal in relationship of sodium to chloride reported by Conn[6] did not uniformly occur. This variation may be related to dosage. A patient with treated Addison's disease showed sweat sodium and chloride concentrations of 83.5 and 73.0 mEq./L., respectively, both well above the normal range. Similarly, a patient with hypopituitarism exhibited concentrations of 83.0 and 61.0 mEq./L. These findings are in agreement with Conn's original observations.

SUMMARY

A simplified method for obtaining thermal sweat is described. Analysis of sweat obtained by this method affords a valid clinical index of one phase of adrenal cortical activity.

REFERENCES

1. KUNO, Y. Physiology of Human Perspiration. London, 1934. J. & A. Churchill.
2. DILL, D. B. Life, Heat and Altitude. Cambridge, 1938. Harvard University Press.
3. MCCANCE, R. A. The effect of salt deficiency in man on the volume of the extracellular fluids and on the composition of sweat, saliva, gastric juice and cerebrospinal fluid. *J. Physiol.*, 92: 208–218, 1938.
4. KEUTMANN, E. H., BASSETT, S. H. and WARREN, S. L. Electrolyte balances during artificial fever with special reference to loss through the skin. *J. Clin. Investigation*, 18: 239–250, 1939.
5. CONN, J. W. and JOHNSTON, M. W. The function of the sweat glands in the economy of NaCl under conditions of hard work in a tropical climate. *J. Clin. Investigation*, 29: 933, 1944.
6. CONN, J. W. Electrolyte composition of sweat. *Arch. Int. Med.*, 83: 416–428, 1949.
7. GIBBON, J. H. and LANDIS, E. M. Vasodilatation in the lower extremities in response to immersing the forearms in warm water. *J. Clin. Investigation*, 11: 1019–1036, 1932.
8. PICKERING, G. W. The peripheral resistance in persistent arterial hypertension. *Clin. Sc.* 2: 209–235, 1936.
9. MENDLOWITZ, M. Measurements of blood flow and blood pressure in clubbed fingers. *J. Clin. Investigation*, 20: 113–117, 1941.
10. GOETZ, R. H. and AMES, F. Reflex vasodilatation by body heating in diagnosis of peripheral vascular disorders: a criticism of methods. *Arch. Int. Med.*, 84: 396–418, 1949.
11. DILL, D. B., HALL, F. G. and EDWARDS, F. P. Changes in composition of sweat during acclimatization to heat. *Am. J. Physiol.*, 123: 412–419, 1938.
12. SENDROY, J., JR. Photoelectric microdetermination of chloride in biological fluids, and of iodate and iodine in protein-free solutions. *J. Biol. Chem.*, 130: 605–623, 1939.
13. KINGSLEY, G. R. and DOWDELL, L. A. Direct iodometric colorimetric determination of blood chloride. In press, (*J. Lab. Clin. Med.*).

AUTHOR INDEX VOLUME VIII

Alexander, Benjamin, 255
Anderson, Harold C., 445
Armentrout, H. L., 246

Baker, A. B., 153
Bechgaard, Poul, 53
Bello, C. T., 634
Berger, James S., 724
Berlin, Irving, 552
Berman, Bernard, 480
Best, William R., 124
Bevans, Margaret, 401
Bickerman, Hylan A., 263
Bittner, John J., 218
Black, Jack, 412
Block, Matthew, 710
Borden, Craig W., 701
Bothereau, N. R., 733
Bower, Albert G., 160
Brody, Henry, 675
Brixey, A. M., Jr., 738
Brown, Thomas McP., 421
Burchenal, Joseph H., 767
Burke, Richard M., 738
Burwell, Walter Brodie, 640

Clark, Thomas E., 180, 187
Collins, Harvey S., 4, 21
Conn, James J., 180, 187
Coodley, Eugene L., 816
Cosby, Richard S., 169, 177
Cosgriff, Stuart W., 57

Daniels, Worth B., 468
Davis, Frank W., Jr., 131
Dolger, Henry, 285
Doscher, Ned, 623
Dragstedt, Lester R., 409
Duran-Reynals, F., 490

Ebert, Richard V., 701
Edmeades, Donald T., 474
Erskine, Frederick Adams, 239

Feldman, Daniel J., 552
Ferguson, James J., Jr., 456
Fineberg, Jacob C., 290
Finland, Maxwell, 4, 21

Gambescia, Joseph M., 600
Gardner, Horace T., 561, 565, 584, 591, 600, 611, 614
Glass, George B. Jerzy, 745
Glass, Irving A., 552
Glassy, Frank J., 544
Gocke, Thomas M., 4, 21
Gold, Herman, 31
Gordon, Gilbert L., 332
Gordon, Harold M., 724
Greco, Anthony J., 816
Griffith, George C., 474

Hamilton, Howard, 269
Hammarström, Sven, 53
Hanger, Franklin M., 325
Harris, Charles, 552
Harvey, A. McGehee, 1
Havens, W. Paul, Jr., 559, 591, 614
Hendrix, James P., 640
Hovsepian, Deron, 160
Huddleston, O. Leonard, 160
Hueper, W. C., 355
Hull, John G., 131

Jacobson, Leon O., 710
Jailer, Joseph W., 269

Karnofsky, David A., 767
Kety, Seymour S., 205
Kissane, R. W., 180, 187
Kissin, Milton, 314
Knowlton, Abbie I., 269
Knowlton, Marjorie, 581, 584, 591, 600
Koprowski, Hilary, 412
Kritzler, Robert A., 325

Landis, Francis B., 46
Landwehr, Greta, 255
Lang, Henry, 255
Laszlo, Daniel, 724
Leevy, Carroll M., 290
Leibowitz, Sidney, 314, 675
Leslie, Alan, 823
Levin, Melvin H., 823
Levinson, David C., 474
Levintow, Leon, 584
Levy, Robert L., 34
Lippman, Richard W., 686

Martin, Lay, 196
Mason, James H., Jr., 239
Massey, Franklin C., 544
McCann, William S., 62
McCarty, Maclyn, 445
McDade, Harry, 239
McGuire, Johnson, 480
Mider, G. Burroughs, 71
Miller, Wade N., 581, 591
Modica, Martin, 584
Moore, Douglas J., 614
Moss, W. G., 634

Neefe, John R., 600
Nickerson, Mark, 342

Papp, Jean P., 260
Patek, Arthur J., Jr., 267
Patterson, Myron C., 34
Paul, Jerome T., 124
Paul, John R., 565
Perkins, James G., 115
Petersen, Arthur B., 115
Plough, Irvin C., 401
Poindexter, Charles A., 623
Post, Joseph, 300

Readinger, Harry M., 611
Rice, Raymond L., 691
Riley, James A., 115
Rinzler, Seymour H., 314
Rose, Jerome V., 300
Rothstein, Emil, 46
Ryan, Charles M., 290

Sawitsky, Arthur, 260
Scheinberg, Peritz, 139, 148
Schilaro, Anthony J., 263
Shapiro, Sidney, 153
Sheedy, John A., 611
Slavin, Howard B., 456
Smith, Taylor R., 710
Spurr, Charles L., 710
Stock, C. Chester, 658
Stone, Jacob, 263
Streitfeld, Franklin H., 581, 614
Swift, William E., Jr., 581, 584, 591, 611, 614
Swyer, Alfred J., 724

Turner, Roy H., 689

Underwood, F. J., 246

Van der Scheer, James, 412
Vardell, James C., Jr., 131

Wallace, Stanley L., 552
Weiss, E., 634
Wells, E. Buist, 4, 21
Wells, Herbert S., 701
Werner, Sidney C., 325
West, Randolph, 269
Wichelhausen, Ruth H., 421
Wiener, Louis M., 260
Wilson, Russell H., 701
Wood, W. Barry, 137

Zinn, Willard J., 169, 177

SUBJECT INDEX VOLUME VIII

(E.) = Editorial

ACTH in panhypopituitarism and myxedema, 269
Aerosol penicillin in lung abscess, 263
American Federation for Clinical Research, 393, 805
Amyloidosis in Hodgkin's disease, 552
Anemia
  hemolytic, antibody complicating mononucleosis, 260
  hypoplastic, after anticonvulsant, 124
  with hepatosplenomegaly and cardiac failure, 512
Aneurysm
  arteriovenous, and telangiectasia, 246
  cardiac, 480
  of aorta and abdominal pain, 474
Anthrax, treatment of, with aureomycin, 31
Antirabies serum, hyperimmune, 412
Arterial hypertension, prognosis in, 53
Arthro-onychodysplasia, 738
Aureomycin
  in anthrax, 31
  in atypical pneumonia, 4
  in influenza, 21

Biomorphology, limits of (E.), 137
Blood serum, thermal coagulation point of, 745
Book reviews, 136, 558, 688
Brain
  circulation and metabolism of, 205
  vascular disease of, 139
Bromsulfalein, retention of, in blood, 591

Cancer
  and neoplastic infection, 490
  chemotherapy, clinical, 767
    experimental, 658
  of breast, hypercalcemia in, 724
  research, genetic aspect of, 218
    introduction to, 71
Carcinogens and carcinogenesis, 355
Cardiology, aspects of, 62
Cephalin-cholesterol flocculation test in viral hepatitis, 600
Cerebral
  blood flow in vascular disease of brain, 139
  circulation in heart failure, 148
Chiari's syndrome, 401
Cholecystography, oral, in viral hepatitis, 611
Cholesterol esters in viral hepatitis, 584
Circulatory function of respiration, 62
Circulation of human brain, 205
Cirrhosis
  of liver and mononucleosis, 675
    and acute hepatitis (E.), 267
Clinic on psychosomatic problems (Massachusetts General Hosp.)
  Ulcerative colitis, 789
Clinico-pathologic conferences (Washington Univ.)
  Hematuria, pneumonia and cachexia, 106
  Penicillin-resistant subacute bacterial endocarditis, 794
  Respiratory infection, arthralgia and renal failure, 229
  Severe anemia with hepatosplenomegaly and cardiac failure, 512
  Skin eruption, obtundity and pyrexia, 384
Coagulation
  mechanism of pleural blood, 57
  thermal, of blood serum, 745
Colitis, ulcerative, 789
Colloidal red test in viral hepatitis, 600
Combined staff clinic (Columbia Univ.)
  Inborn errors of metabolism, 90
Conference on therapy (Cornell Univ.)
  Household poisonings II, 372
Cor biloculare, 180
Cor triloculare, 187
C-reactive protein in blood in rheumatic fever, 445
Curare in anterior poliomyelitis, 160

D.H.O. 180 in hypertension, 634
Diabetes
  mellitus and liver dysfunction, 290
  severe, insulin mixtures in, 285
Diaphragm elevation of, and pleural effusion, 46
Diarrhea, chronic, potassium deficiency and, 115
Digitalis poisoning, 640
Dihydroergocornine (D.H.O. 180) in hypertension, 634

Electrocardiogram, accuracy of, 177
Emphysema, pulmonary, hypertension in, 701
Endocarditis, bacterial, penicillin-resistant, 794

Genetic aspect of cancer research, 218

Heart
  failure, cerebral circulation in, 148
  hemangio-endothelial sarcoma of, 544
Hematuria, pneumonia and cachexia, 106
Hemopneumothorax, coagulation of pleural blood in, 57

Hepatic vein occlusion, 401
Hepatitis
  acute, and cirrhosis of liver (E.), 267
  flocculation and related tests in, 600
  viral, endemiology of, 565
    history of in Germany, 561
Hepatosplenomegaly and cardiac failure, 512
Herpes simplex virus and zoster-like eruptions, 456
Hodgkin's disease and amyloidosis, 552
Household poisonings, 372
Hypercalcemia in metastatic cancer of breast, 724
Hypertension
  arterial, 53
  dihydroergocornine in, 634
  pulmonary, in emphysema, 701
  sympathetic blockade in, 342
Hypertonicity, intestinal, 196
Hyperventilation, symptom patterns of, 691
Hypoprothrombinemia, congenital, 255

Infections, respiratory, and aureomycin, 21
Influenza, treatment of, with aureomycin, 21
Infrapulmonary pleural effusion, 46
Insecticides, hazards of (E.), 1
Insulin mixtures in severe diabetes, 285
Intestinal hypomotility and hypertonicity, 196

Jaundice during methyl testosterone therapy, 325

Laboratory and training for internal medicine (E.), 689
Laennec's cirrhosis of liver, 300
Leukemias, nitrogen mustard in, 710
Liver
  cirrhosis of, and mononucleosis, 675
  dysfunction and diabetes mellitus, 290
  Laennec's cirrhosis of, 300
Lung abscess, aerosol penicillin in, 263
Lymphomas, nitrogen mustard in, 710

Meningococcic infection, death in, 468
Metabolism
  inborn errors of, 90
  of human brain, 205
Methyl testosterone and jaundice, 325
Mononucleosis
  and cirrhosis of liver, 675
  infectious, 260
Myocardial infarction, 169, 177, 623
Myxedema, ACTH in, 269

Neoplastic infection and cancer, 490
Nephrotic syndrome with water and salt retention, 686
Neurofibromatosis and pheochromocytoma, 131
Nitrogen mustard in lymphomas and leukemias, 710

Ochronosis, clinical aspects of, 816
Osseous Gaucher's disease, 332

Panhypopituitarism, ACTH in, 269
Paralysis agitans, dihydro-beta-erythroidine in, 153
Pericarditis, serofibrinous, 34
Peritonitis, tuberculous, and streptomycin, 421
Pheochromocytoma with neurofibromatosis, 131
Pneumonia, atypical, and aureomycin, 4
Poisoning by digitalis, 640
Poliomyelitis
  bulbar, 239
  curare in, 160
  perforation of esophageal ulcers in, 239
Potassium deficiency, renal and cardiac lesions in, 115
Prothrombin, conversion of, in hypoprothrombinemia, 255

Rabies, experimental, antirabies serum in, 412
Respiration, circulatory function of, 62
Respiratory infection, arthralgia and renal failure, 229
Rheumatic fever, C-reactive protein in blood in, 445

Sarcoma, hemangio-endothelial, of heart, 544
Secretions, bodily, cytologic study of, 733
Serum cholesterol in viral hepatitis, 584
Skin eruption, obtundity and pyrexia, 384
Stellate ganglion block, 139
Streptomycin in tuberculous peritonitis, 421
Sweat test for clinical use, 823
Sympathectomy and arterial hypertension, 53
Sympathetic blockade in hypertension, 342
Symptom patterns of hyperventilation, 691

Telangiectasia, hemorrhagic, and arteriovenous aneurysm, 246
Thromboses, venous, multiple, 401
Thymol test in viral hepatitis, 600

Vagotomy for peptic ulcer (E.), 409
Viral hepatitis
  course of, and convalescence, 614
  in Germany, 561
  oral cholecystography in, 611
  retention of bromsulfalein in, 591
  screening tests for, 581
  serum cholesterol in, 584

Weil's disease, 314
Western Society for Clinical Research, 522

Zoster-like eruptions caused by herpes simplex virus, 456

The American Journal of Medicine

Editor ALEXANDER B. GUTMAN, M. D.

Professor of Medicine, COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS, NEW YORK

ADVISORY BOARD

Chairman: WALTER W. PALMER, M.D., *Bard Professor Emeritus*, Columbia University College of Physicians and Surgeons, *New York;* DAVID P. BARR, M.D., *Professor of Medicine*, Cornell University Medical College, *New York;* ARTHUR L. BLOOMFIELD, M.D., *Professor of Medicine*, School of Medicine, Stanford University, *San Francisco;* FRANCIS G. BLAKE, M.D., *Sterling Professor of Medicine*, Yale University School of Medicine, *New Haven;* EUGENE A. STEAD, JR., M.D., *Professor of Medicine*, School of Medicine, Duke University, *Durham;* JOSEPH T. WEARN, M.D., *Professor of Medicine*, School of Medicine, Western Reserve University, *Cleveland.*

ASSOCIATE EDITORS

HERRMAN L. BLUMGART, M.D., *Boston;* HARRY GOLD, M.D., *New York;* A. MCGEHEE HARVEY, M.D., *Baltimore;* GEORGE H. HOUCK, M.D., *Palo Alto;* CHESTER S. KEEFER, M.D., *Boston;* T. GRIER MILLER, M.D., *Philadelphia;* WALTER L. PALMER, M.D., *Chicago;* OSWALD H. ROBERTSON, M.D., *Chicago;* EPHRAIM SHORR, M.D., *New York;* GEORGE W. THORN, M.D., *Boston;* WILLIAM S. TILLETT, M.D., *New York;* ROY H. TURNER, M.D. *New Orleans;* RUSSELL M. WILDER, M.D., *Rochester;* M. M. WINTROBE, M.D., *Salt Lake City;* W. BARRY WOOD, M.D., *St. Louis;* JOHN B. YOUMANS, M.D., *Chicago.*

Volume VIII

JANUARY TO JUNE

1950

THE AMERICAN JOURNAL OF MEDICINE, INC.

NEW YORK MCML

CONTENTS OF VOLUME VIII

ORIGINAL ARTICLES

Potential Hazards of the Newer Insectides	*A. McGehee Harvey*	1
Treatment of Primary Atypical Pneumonia with Aureomycin	*Harvey S. Collins, E. Buist Wells, Thomas M. Gocke, Maxwell Finland*	4
Aureomycin in the Treatment of Influenza and Certain Other Acute Respiratory Infections with or without Pneumonia	*Maxwell Finland, E. Buist Wells, Harvey S. Collins, Thomas M. Gocke*	21
Aureomycin in the Treatment of Anthrax	*Herman Gold*	31
Acute Serofibrinous Pericarditis of Undetermined Cause. A Study of Twenty-seven Cases	*Robert L. Levy, Myron C. Patterson*	34
Infrapulmonary Pleural Effusion Simulating Elevation of the Diaphragm	*Emil Rothstein, Francis B. Landis*	46
Prognosis in Arterial Hypertension. Comparison between 251 Patients after Sympathectomy and a Selected Series of 435 Non-operated Patients	*Sven Hammarström, Poul Bechgaard*	53
Study of the Coagulation Mechanism of Pleural Blood in Hemopneumothorax	*Stuart W. Cosgriff*	57
Some Neglected Aspects of Cardiology. Circulatory Function of the Respiration	*William S. McCann*	62
An Introduction to Cancer Research	*G. Burroughs Mider*	71
Inborn Errors of Metabolism		90
Hematuria, Pneumonia and Cachexia		106
Renal and Cardiac Lesions in Potassium Deficiency Due to Chronic Diarrhea	*James G. Perkins, Arthur B. Petersen, James A. Riley*	115
Severe Hypoplastic Anemia Following Anticonvulsant Medication. Review of the Literature and Report of a Case	*William R. Best, Jerome T. Paul*	124
Pheochromocytoma with Neurofibromatosis	*Frank W. Davis, Jr., John G. Hull, James C. Vardell, Jr.*	131
The Limits of Biomorphology	*W. Barry Wood*	137
Cerebral Blood Flow in Vascular Disease of the Brain. With Observations on the Effects of Stellate Ganglion Block	*Peritz Scheinberg*	139
Cerebral Circulation in Heart Failure	*Peritz Scheinberg*	148
Treatment of Paralysis Agitans with Dihydro-beta-erythroidine	*Sidney Shapiro, A. B. Baker*	153
Use of Curare in the Treatment of Anterior Poliomyelitis	*Albert G. Bower, O. Leonard Huddleston, Deron Hovsepian*	160
Myocardial Infarction. I. Statistical Analysis of 679 Autopsy-proven Cases	*Willard J. Zinn, Richard S. Cosby*	169
Myocardial Infarction. II. A Re-evaluation of the Diagnostic Accuracy of the Electrocardiogram	*Willard J. Zinn, Richard S. Cosby*	177

Cor Biloculare. Report of Four Cases	*James J. Conn, Thomas E. Clark, R. W. Kissane*	180
Cor Trilocular. Report of Four Cases	*James J. Conn, Thomas E. Clark, R. W. Kissane*	187
Observations on Small Intestinal Hypomotility and States of Hypertonicity Arising from Functional Bases	*Lay Martin*	196
Circulation and Metabolism of the Human Brain in Health and Disease	*Seymour S. Kety*	205
Genetic Aspect of Cancer Research	*John J. Bittner*	218
Respiratory Infection, Arthralgia and Renal Failure		229
Perforation of Esophageal Ulcers in Bulbar Poliomyelitis. Report of Two Fatal Cases	*Frederick Adams Erskine, James H. Mason, Jr., Harry McDade*	239
Familial Hemorrhagic Telangiectasia with Associated Pulmonary Arteriovenous Aneurysm	*H. L. Armentrout, F. J. Underwood*	246
Congenital Hypoprothrombinemia. A Case Study with Particular Reference to the Role of Non-prothrombin Factors in the Conversion of Prothrombin	*Greta Landwehr, Henry Lang, Benjamin Alexander*	255
The Demonstration of Antibody in Acute Hemolytic Anemia Complicating Infectious Mononucleosis	*Arthur Sawitsky, Jean P. Papp, Louis M. Wiener*	260
Aerosol Penicillin in the Treatment of Chronic Lung Abscess	*Hylan A. Bickerman, Jacob Stone, Anthony J. Schilaro*	263
Relation of Acute Hepatitis to Cirrhosis of the Liver	*Arthur J. Patek, Jr.*	267
Effects of Pituitary Adrenocorticotrophic Hormone (ACTH) in Panhypopituitarism of Long-standing and in Myxedema	*Abbie I. Knowlton, Joseph W. Jailer, Howard Hamilton, Randolph West*	269
Prepared Insulin Mixtures in the Treatment of the Severe Diabetic Patient	*Henry Dolger*	285
Diabetes Mellitus and Liver Dysfunction. Etiologic and Therapeutic Considerations	*Carroll M. Leevy, Charles M. Ryan, Jacob C. Fineberg*	290
Clinical, Functional and Histologic Studies in Laennec's Cirrhosis of the Liver	*Joseph Post, Jerome V. Rose*	300
Weil's Disease. Report of Five Cases	*Sidney Leibowitz, Milton Kissin, Seymour H. Rinzler*	314
Jaundice during Methyl Testosterone Therapy	*Sidney C. Werner, Franklin M. Hanger, Robert A. Kritzler*	325
Osseous Gaucher's Disease. Report of Two Cases in Siblings	*Gilbert L. Gordon*	332
Role of Sympathetic Blockade in the Therapy of Hypertension	*Mark Nickerson*	342
Carcinogens and Carcinogenesis	*W. C. Hueper*	355
Household Poisonings II		372
Skin Eruption, Obtundity and Pyrexia		384

Contents

American Federation for Clinical Research—Abstracts of Papers Presented at the Eastern Sectional Meeting in Boston, December 3, 1949		393
Chiari's Syndrome: Hepatic Vein Occlusion. A Case of Multiple Venous Thromboses	*Irvin C. Plough* *Margaret Bevans*	401
Vagotomy for Peptic Ulcer. A Reply	*Lester R. Dragstedt*	409
Use of Hyperimmune Antirabies Serum Concentrates in Experimental Rabies	*Hilary Koprowski* *James Van der Scheer* *Jack Black*	412
Tuberculous Peritonitis Treated with Streptomycin	*Ruth H. Wichelhausen* *Thomas McP. Brown*	421
Determination of C-reactive Protein in the Blood as a Measure of the Activity of the Disease Process in Acute Rheumatic Fever	*Harold C. Anderson* *Maclyn McCarty*	445
Zoster-like Eruptions Caused by the Virus of Herpes Simplex	*Howard B. Slavin* *James J. Ferguson, Jr.*	456
The Western Society for Clinical Research. Abstracts of Papers Presented at the Third Annual Meeting, Salt Lake City, January 27 and 28, 1950		522
Primary Hemangio-endothelial Sarcoma of the Heart	*Capt. Frank J. Glassy* *Franklin C. Massey*	544
Amyloidosis in Hodgkin's Disease	*Stanley L. Wallace* *Daniel J. Feldman* *Irving Berlin* *Charles Harris* *Irving A. Glass*	552
Foreword	*W. Paul Havens, Jr.*	559
A Note on the History of Epidemic Viral Hepatitis in Germany	*Horace T. Gardner*	561
Endemiologic Aspects of Hepatitis in U. S. Troops in Germany 1946–1950	*John R. Paul* *Horace T. Gardner*	565
An Evaluation of Two Screening Tests for the Detection of Early and Sub-icteric Viral Hepatitis	*William E. Swift, Jr.* *Wade N. Miller* *Franklin H. Streitfeld* *Marjorie Knowlton*	581
Serum Cholesterol and Cholesterol Esters in Viral Hepatitis	*Horace T. Gardner* *William E. Swift, Jr.* *First Lt. Martin Modica* *Leon Levintow* *Marjorie Knowlton*	584
Factors Influencing Retention of Bromsulfalein in the Blood of Patients with Viral Hepatitis	*W. Paul Havens, Jr.* *Wade N. Miller* *William E. Swift, Jr.* *Horace T. Gardner* *Marjorie Knowlton*	591
Comparison of the Thymol, Cephalin-cholesterol Flocculation and Colloidal Red Tests in Acute Viral Hepatitis	*John R. Neefe* *Joseph M. Gambescia* *Horace T. Gardner* *Marjorie Knowlton*	600

Contents

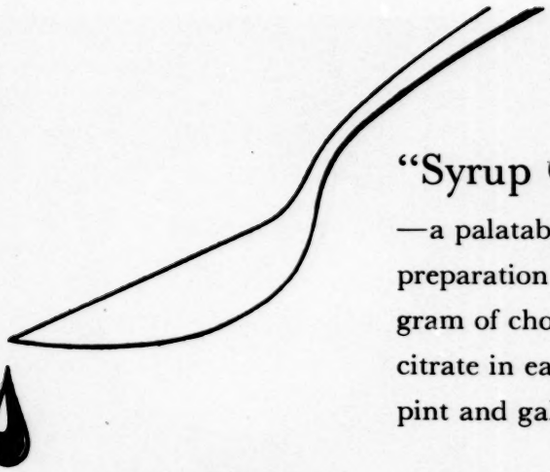
Oral Cholecystography in Patients with Viral Hepatitis	*Harry M. Readinger, William E. Swift, Jr., Horace T. Gardner, John A. Sheedy*	611
Clinical Course of Viral Hepatitis and the Effect of Exercise during Convalescence	*William E. Swift, Jr., Horace T. Gardner, Douglas J. Moore, Franklin H. Streitfeld, W. Paul Havens, Jr.*	614
Myocardial Infarction without Anticoagulant Therapy. Deaths, Emboli and an Analysis of Factors Influencing Mortality	*Ned Doscher, Charles A. Poindexter*	623
Effect of Orally Administered Dihydroergocornine (D.H.O. 180) on Hypertension	*C. T. Bello, W. G. Moss, E. Weiss*	634
Digitalis Poisoning	*Walter Brodie Burwell, James P. Hendrix*	640
Aspects of Approaches in Experimental Cancer Chemotherapy	*C. Chester Stock*	658
Cirrhosis of the Liver Following Infectious Mononucleosis	*Sidney Leibowitz, Henry Brody*	675
Nephrotic Syndrome with Exaggerated Premenstrual Water and Salt Retention	*Richard W. Lippman*	686
The Clinical Laboratory and Training for Internal Medicine	*Roy H. Turner*	689
Symptom Patterns of the Hyperventilation Syndrome	*Raymond L. Rice*	691
Pulmonary Hypertension in Chronic Pulmonary Emphysema	*Craig W. Borden, Russell H. Wilson, Richard V. Ebert, Herbert S. Wells*	701
The Role of Nitrogen Mustard Therapy in the Treatment of Lymphomas and Leukemias	*Charles L. Spurr, Taylor R. Smith, Matthew Block, Leon O. Jacobson*	710
Hypercalcemia in Osteolytic Metastatic Cancer of the Breast	*Alfred J. Swyer, Capt. James S. Berger, Harold M. Gordon, Daniel Laszlo*	724
Use of Paraffin-embedding Methods in the Cytologic Study of Various Bodily Secretions	*N. R. Bothereau*	733
Arthro-onychodysplasia. Hereditary Syndrome Involving Deformity of Head of Radius, Absence of Patellas, Posterior Iliac Spurs, Dystrophy of Finger Nails	*A. M. Brixey, Jr., Richard M. Burke*	738
The Thermal Coagulation Point of Blood Serum		
I. Method and Clinical Interpretation	*George B. Jerzy Glass*	745
II. Significance of the Principle of Defective Thermal Coagulation for Diagnosis of Cancer		755
III. Correlation with Serum Proteins, Sedimentation Rate and Weltmann Reaction		759

Contents

Present Status of Clinical Cancer Chemotherapy	*David A. Karnofsky*, *Joseph H. Burchenal*	767
Ulcerative Colitis		789
Penicillin-resistant Subacute Bacterial Endocarditis		794
American Federation for Clinical Research—Abstracts of Papers Presented at the Seventh Annual Meeting of the Midwestern Section Held in Chicago, November 3, 1949		805
Clinical Aspects of Ochronosis. With Report of a Case	*Eugene L. Coodley*, *Anthony J. Greco*	816
Sweat Test Simplified for Clinical Use	*Alan Leslie*, *Melvin H. Levin*	823

COPYRIGHT, 1950
BY THE AMERICAN JOURNAL OF MEDICINE, INC.
All Rights Reserved

Printed in the United States of America



"Syrup Choline (*Flint*)"
—a palatable and stable preparation containing one gram of choline dihydrogen citrate in each 4 cc. Supplied in pint and gallon bottles.

SYRUP Choline

CAPSULES

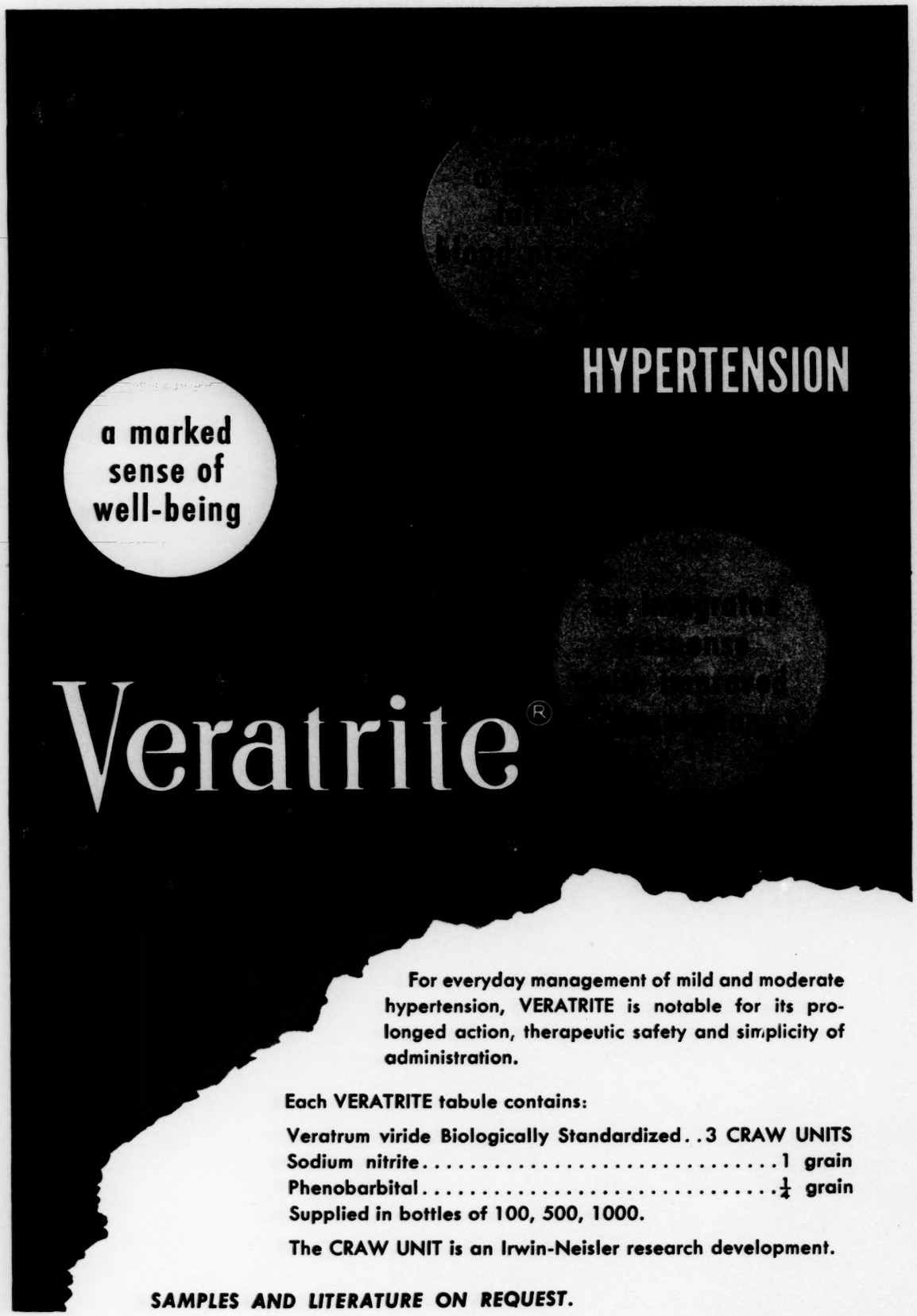
"Capsules Choline (*Flint*)"
—containing 0.5 gram of choline dihydrogen citrate per capsule. Supplied in bottles of 100, 500 and 1000.

"Choline (Flint)" is indicated in the treatment of chronic liver involvement in diabetes, in malnutrition, in poisoning by hepatoxic agents, in various infectious processes and in cirrhosis.

For your copy of "The Present Status of Choline Therapy in Liver Dysfunction"—write

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

FLINT, EATON & COMPANY
DECATUR, ILLINOIS



For everyday management of mild and moderate hypertension, VERATRITE is notable for its prolonged action, therapeutic safety and simplicity of administration.

Each VERATRITE tabule contains:

Veratrum viride Biologically Standardized..3 CRAW UNITS
Sodium nitrite.....1 grain
Phenobarbital.....¼ grain
Supplied in bottles of 100, 500, 1000.

The CRAW UNIT is an Irwin-Neisler research development.

SAMPLES AND LITERATURE ON REQUEST.

ORETON

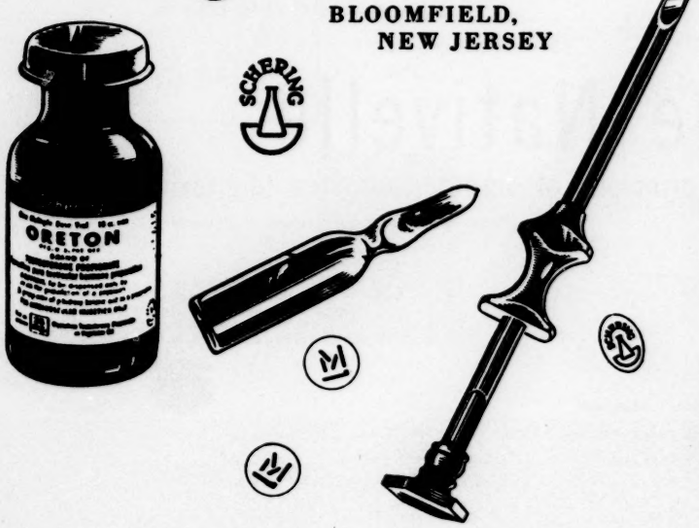
ORETON

merely as a substitute for lacking androgenic hormone, ORETON® preparations have today reached new therapeutic horizons.

As a general stimulus to protein anabolism and as a means of conserving tissue nitrogen, ORETON finds wide usefulness in certain states of debility and in checking the metabolic deterioration of senescence. ORETON has established itself firmly for palliative treatment of female breast carcinoma, endometriosis, functional uterine bleeding and dysmenorrhea.

Schering CORPORATION

BLOOMFIELD,
NEW JERSEY



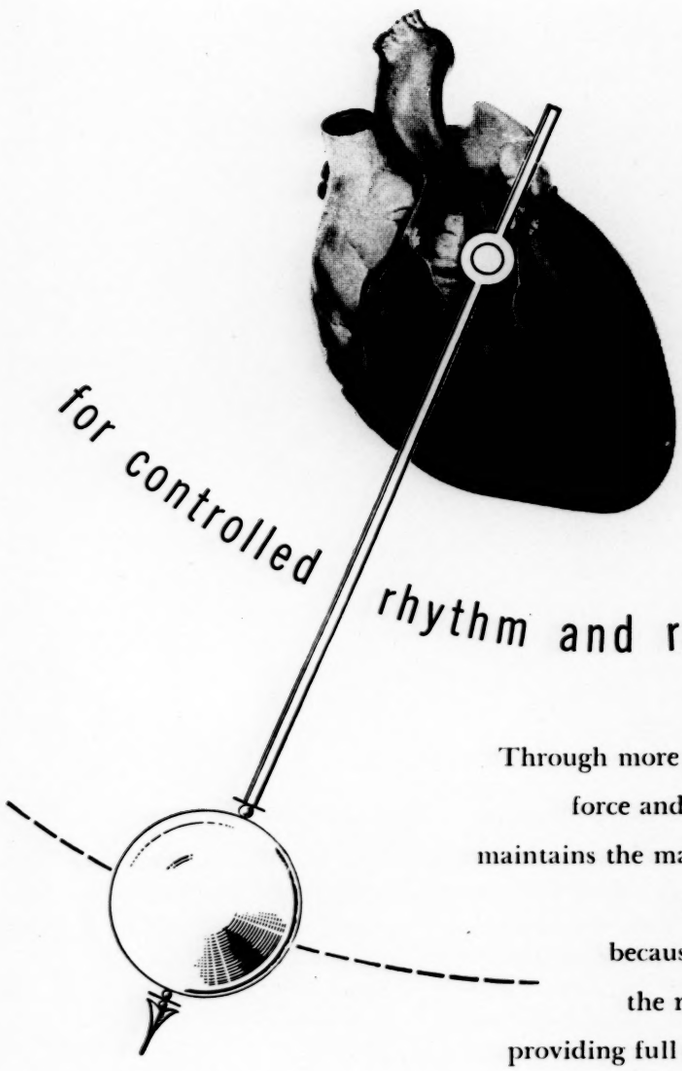
ORETON
(testosterone propionate)

ORETON Buccal Tablets
(testosterone propionate)

ORETON-M® Tablets
(methyltestosterone)

ORETON-F® Pellets
(free testosterone)

ORETON-M Ointment
(methyltestosterone)



for controlled rhythm and rate . . .

Through more precise control of contractile force and rhythm, Digitaline Nativelle maintains the maximum efficiency obtainable. *This maintenance is positive* because *absorption is complete* and the rate of *dissipation is uniform;* providing full digitalis effect between doses. All, with virtual freedom from untoward side effects.

Digitaline Nativelle

Chief active principle* of digitalis purpurea (digitoxin)

**Not an adventitious mixture of glycosides*

Send for new brochure . . . "Modern Digitalis Therapy," Varick Pharmacal Co., Inc. (Div. of E. Fougera & Co., Inc.) 75 Varick St., New York, N.Y.

MAINTENANCE: 0.1 or 0.2 mg. daily depending upon patient's response.
CHANGE-OVER: 0.1 or 0.2 mg. of Digitaline Nativelle replaces 0.1 gm. or 0.2 gm. whole leaf.
RAPID DIGITALIZATION: 0.6 mg. initially, followed by 0.2 or 0.4 mg. every 3 hours until patient is digitalized.

Indication:

HAY FEVER

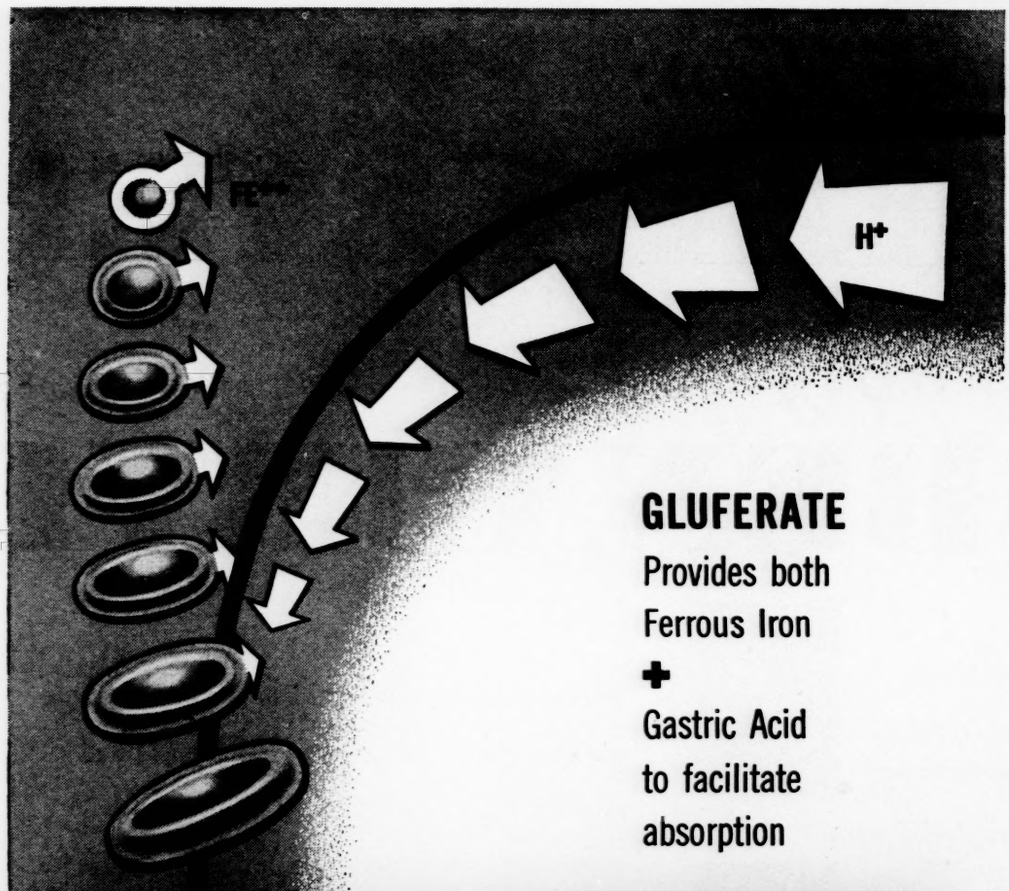
Therapy:

BENADRYL®

This is the season when bleary-eyed, sneezing patients turn to you for the rapid, sustained relief of their hay fever symptoms which BENADRYL provides.

Today, for your convenience and ease of administration, BENADRYL Hydrochloride (diphenhydramine hydrochloride, Parke-Davis) is available in a wider variety of forms than ever before including Kapseals®, Capsules, Elixir and Steri-Vials®.

MEDICAMENTA VERA · PD & CO.



GLUFERATE
Provides both
Ferrous Iron
✚
Gastric Acid
to facilitate
absorption

Of the three factors that favor absorption of iron:[1]
(1) Iron in the ferrous state;
(2) Acid reaction in the stomach;
(3) Increased need for iron.

GLUFERATE®

Ferrous Sulfate and Glutamic Acid Hydrochloride Wyeth
provides *both* of the external factors

Ferrous Sulfate—A most efficiently absorbed form of iron.
Glutamic Acid Hydrochloride—Potent in correction of hypoacidity; assures prompt benefit with minimal distress.

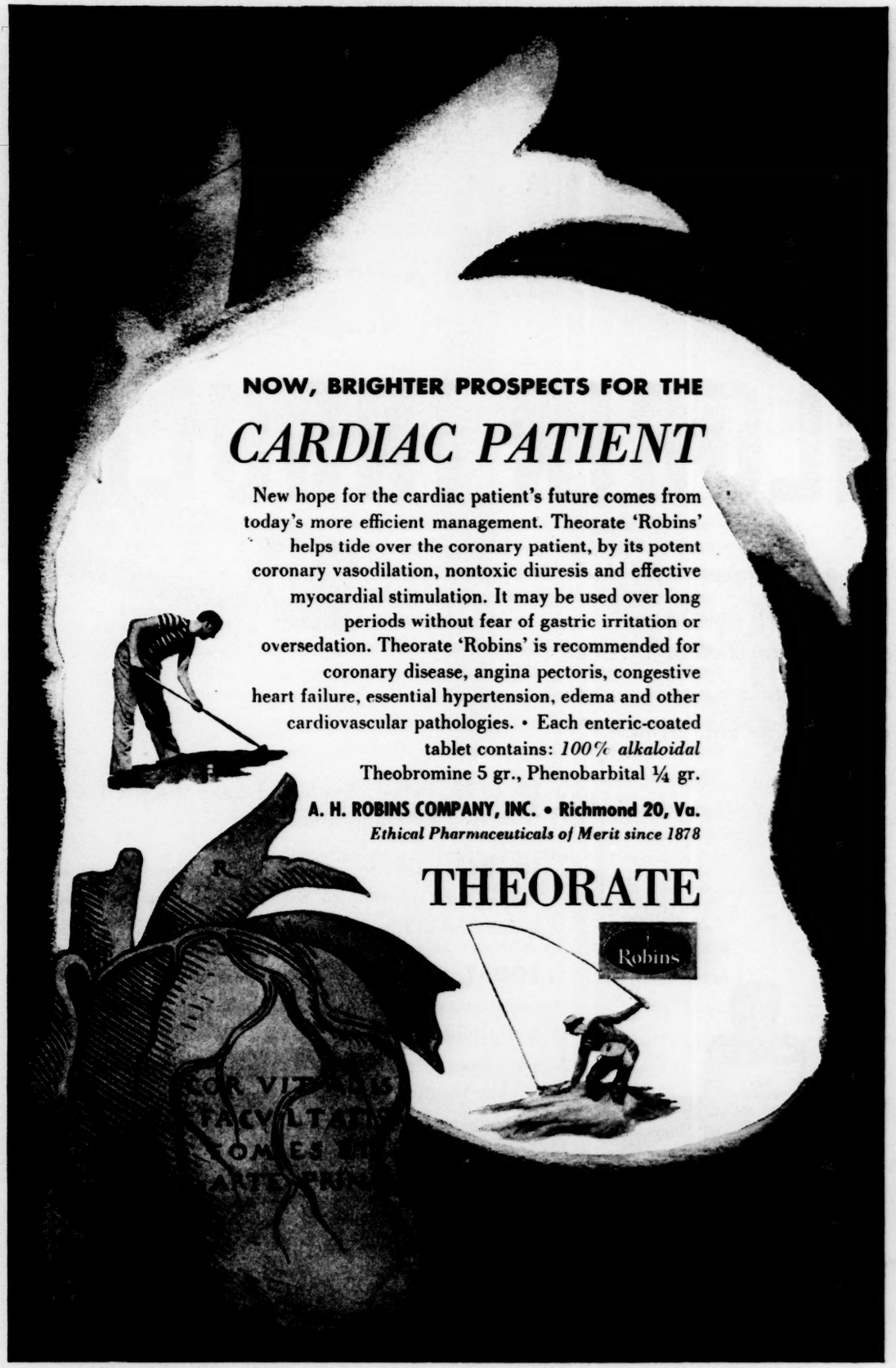
SUPPLIED: Bottles of 100 tablets

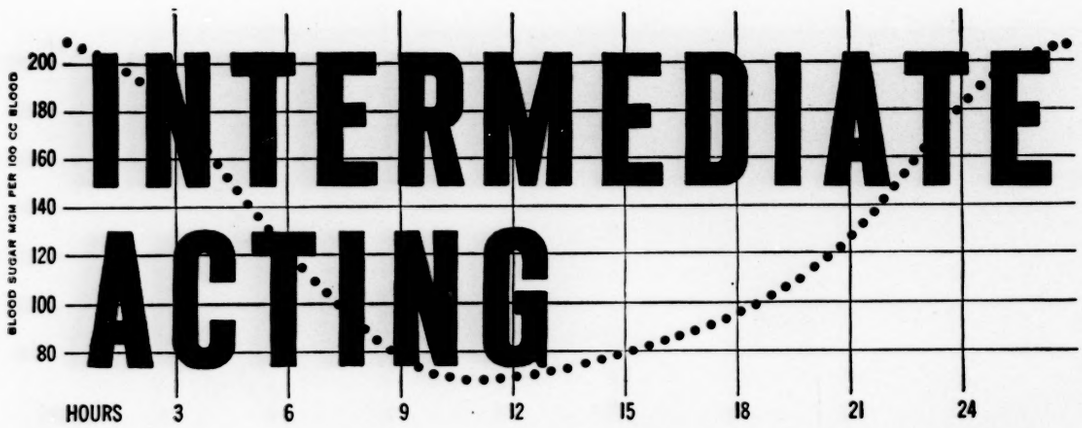
1. Barer, A. P., and Fowler, W. M.: J. Lab. & Clin. Med. 34:932, 1949.

for
"double
insurance"
in
iron-deficiency
anemias

Wyeth Incorporated • Philadelphia 3, Pa.

Wyeth


NOW, BRIGHTER PROSPECTS FOR THE
CARDIAC PATIENT
New hope for the cardiac patient's future comes from today's more efficient management. Theorate 'Robins' helps tide over the coronary patient, by its potent coronary vasodilation, nontoxic diuresis and effective myocardial stimulation. It may be used over long periods without fear of gastric irritation or oversedation. Theorate 'Robins' is recommended for coronary disease, angina pectoris, congestive heart failure, essential hypertension, edema and other cardiovascular pathologies. • Each enteric-coated tablet contains: 100% alkaloidal Theobromine 5 gr., Phenobarbital ¼ gr.
A. H. ROBINS COMPANY, INC. • Richmond 20, Va.
Ethical Pharmaceuticals of Merit since 1878
THEORATE
Robins



INTERMEDIATE ACTING

GLOBIN INSULIN

'B.W.& CO.'

...was developed to fill the "need for an insulin with activity intermediate between that of regular insulin and that of protamine zinc insulin."[1]

IN 1939, Reiner, Searle and Lang described a new "intermediate acting" insulin.

IN 1943, after successful clinical testing, the new substance was released to the profession as 'Wellcome' brand Globin Insulin with Zinc 'B.W. & Co.'

TODAY, according to Rohr and Colwell, "Fully 80% of all severe diabetics can be balanced satisfactorily"[2] with Globin Insulin 'B.W. & Co.'—or with a 2:1 mixture of regular insulin: protamine zinc insulin. *Ready-to-use* Globin Insulin 'B.W. & Co.' provides the desired intermediate action without preliminary mixing in vial or syringe.

In 10 cc. vials, U-40 and U-80.

'B.W.& CO. —a mark to remember

1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. ibid Proc. Am. Diabetes Assn. 8:37, 1948.

BURROUGHS WELLCOME & CO. (U.S.A.) INC. Tuckahoe 7, New York

THE LINING OF THE GALL BLADDER

When inflamed, the gall bladder lining becomes thickened and coarse to a variable degree. Biliary stasis is believed to be a major factor in inciting a catarrhal inflammation which, with secondary infection, may progress to a more virulent cholecystitis with or without cholelithiasis.

DEHYDROCHOLIC ACID ARMOUR

a powerful hydrocholagogue and choleretic, effects a physiologic "flushing-out" of the biliary tract by inducing a copious outflow of thin watery bile low in total solids. It is of value in chronic gall-bladder cases with or without stones (provided there is no actual obstruction) . . . in functional hepatic insufficiency, in liver poisoning by drugs or anesthetics, in cirrhosis, in chronic passive congestion of the liver. It is contra-indicated in obstructive jaundice.

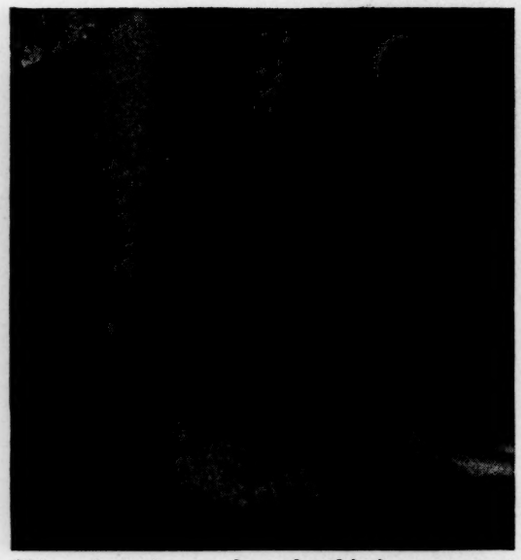
Supplied in 3¾ grain tablets—bottles of 50, 100, 500. Dosage 1 to 3 tablets t.i.d. with meals. Literature on request.

Have confidence in the preparation you prescribe — specify "Armour"

ARMOUR Laboratories

HEADQUARTERS FOR MEDICINALS OF ANIMAL ORIGIN • CHICAGO 9, ILLINOIS

Varicose ulcers of nineteen years' duration. This is one of a series of 50 chronic ulcer cases in which the results of Chloresium Therapy were observed by a leading clinic.



Chloresium therapy brought this improvement in six weeks. Complete healing occurred one month later. Of the fifty cases studied, forty-eight showed marked improvement.

For diabetic and varicose ulcers ... use Chloresium Therapy

Stimulates growth of normal healthy tissue, gives symptomatic relief, deodorizes ... clinically proved.

● In chronic, indolent ulcers, the *problem* is how to aid the healing of tissue which is obviously not able to repair itself. The *answer* is Chloresium, the therapeutic *chlorophyll* preparations. Clinical reports on large series of such cases, which resisted other method of treatment, show that most of them responded rapidly to Chloresium's chlorophyll therapy—and healed completely in relatively short time.

***From the Lahey Clinic Bulletin** (Vol. 4, No. 8, April 1946): "The water-soluble chlorophyll containing ointment (*Chloresium*) has now been used at this clinic in more than 50 cases of the more chronic and difficult ulcers . . . (it) apparently excels any of the previously used agents . . . Many patients who had ulcers unhealed from one to eight years obtained complete healing in six to ten weeks."

***From the Guthrie Clinic Bulletin** (Vol. 16, No. 1, July 1946): "We have used a water-soluble ointment of chlorophyll (*Chloresium*) in a variety of conditions . . . with splendid results in a vast majority of cases. In a group of chronic ulcers there has been almost universal prompt and early healing."

Try Chloresium on your most resistant case—it is nontoxic, bland, soothing, deodorizing.

*Complete reprints available on request.

Chloresium

Therapeutic chlorophyll preparations

Solution (Plain); Ointment; Nasal and Aerosol Solutions

Ethically promoted—at leading drugstores

U. S. Pat. 2,120,667 — Other Pats. Pend.

FREE—CLINICAL SAMPLES

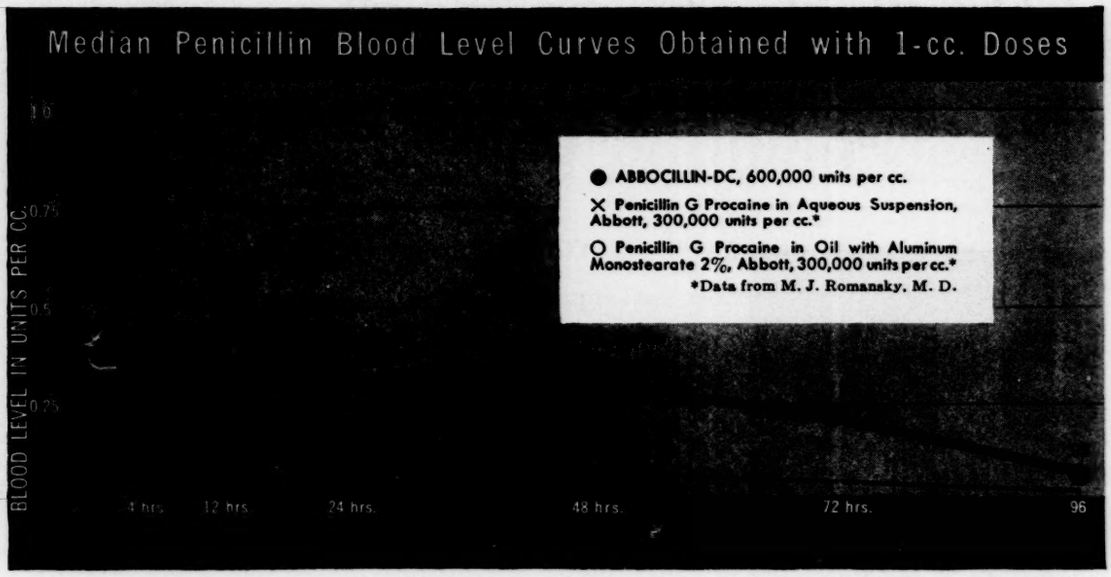
RYSTAN CO., INC., Dept. JM-5
7 N. MacQuesten Pkwy., Mt. Vernon, N. Y.

I want to try Chloresium Ointment and Chloresium Solution (Plain). Please send clinical samples.

*Dr.*_____

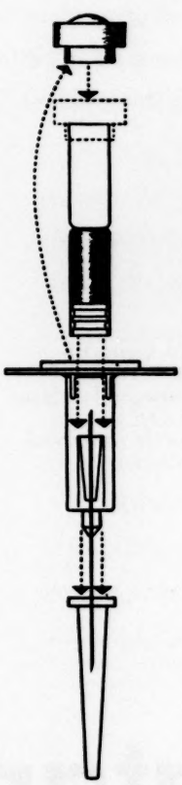
*Address*_____

*City*_____ *Zone*____ *State*_____


Median Penicillin Blood Level Curves Obtained with 1-cc. Doses
BLOOD LEVEL IN UNITS PER CC.
1.0
0.75
0.5
0.25
4 hrs.
12 hrs.
24 hrs.
48 hrs.
72 hrs.
96
● ABBOCILLIN-DC, 600,000 units per cc.
× Penicillin G Procaine in Aqueous Suspension, Abbott, 300,000 units per cc.*
○ Penicillin G Procaine in Oil with Aluminum Monostearate 2%, Abbott, 300,000 units per cc.*
*Data from M. J. Romansky, M. D.

ABBOTT'S *NEW* "DOUBLE CONCENTRATION"

AQUEOUS SUSPENSION OF PENICILLIN G PROCAINE



True Repository Therapy

1 cc.

has consistently afforded sustained high penicillin blood levels

Abbocillin-DC

REG. U. S. PAT. OFF.

Penicillin G Procaine in Aqueous Suspension

600,000 UNITS

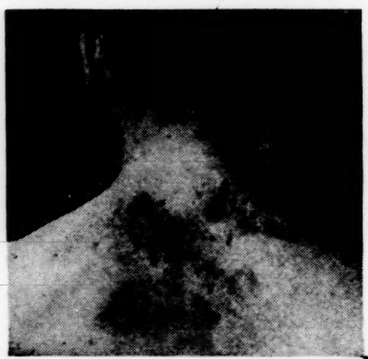
in B-D* 1-cc. Disposable Cartridge Syringe

For intramuscular use only

*T.M. Reg. Becton Dickinson & Co.

ABBOTT LABORATORIES • NORTH CHICAGO, ILLINOIS

highly effective in an unusually wide range of common skin disorders



Pragmatar is particularly useful in seborrheic dermatitis, and in the general care and hygiene of the seborrheic scalp.

Pragmatar often brings dramatic improvement in the common fungous infections—even in "athlete's foot."

Pragmatar is extremely valuable in eczematous eruptions, especially those in which a seborrheic factor is involved.

Smith, Kline & French Laboratories, Philadelphia

Pragmatar

the outstanding tar-sulfur-salicylic acid ointment

The Protein-Rich Breakfast and Morning Stamina

Extensive studies* by the Bureau of Human Nutrition have established that breakfasts rich in protein and supplying 500 to 700 calories, effectively promote a sense of well-being, ward off fatigue, and sustain blood sugar levels at normal values for the entire morning postbreakfast period.

These physiologic advantages are related mainly to the protein content rather than to the caloric content of the breakfast. In fact, when isocaloric breakfasts were compared, those with the higher amounts of protein led to the greatest beneficial effects. Breakfasts providing the lower quantities of protein (7 Gm., 9 Gm., 16 Gm., and 17 Gm. respectively) produced a rapid rise in the blood sugar level and a return to normal during the next three hours. Breakfasts providing more protein (22 Gm. and 25 Gm. respectively) produced a maximal blood sugar rise which was lower than that following the breakfasts of lower protein content, but the return to normal was delayed beyond the three hour period.

The subjects on the higher protein breakfasts "reported a prolonged sense of well-being and satisfaction." The findings indicated that the beneficial effects of the high protein breakfast on the blood sugar level may extend into the afternoon.

Meat, man's preferred protein food, is a particularly desirable means of increasing the protein contribution of breakfast. The many breakfast meats available are not only temptingly delicious and add measurably to the gustatory appeal and variety of the morning meal, but they also provide biologically complete protein, B-complex vitamins, and essential minerals. *Meat for breakfast, a time-honored American custom, is sound nutritional practice.*

---

*Orent-Keiles, E., and Hallman, L. F.: The Breakfast Meal in Relation to Blood-Sugar Values, Circular No. 827, United States Department of Agriculture, Bureau of Human Nutrition and Home Economics, Agricultural Research Administration, Dec., 1949.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute

Main Office, Chicago...Members Throughout the United States

to potency—

and economy

add a sense of Well-Being

ORADIAL is estradiol, the follicular hormone naturally present in the ovary, coupled to an ethinyl group. The resulting man-made hormone is one of the most potent oral estrogens known. Economical lower dosage result from this high potency. Even more important, ORADIAL, being closely related to the natural hormone, confers that woman-wanted *sense of well-being* characteristic only of estrogens derived from natural sources.

Van Pelt & Brown, Inc., Richmond, Virginia

Supplied: Tablets of 0.02 mg. and 0.05 mg. in bottles of 30 and 100.

VB

ORADIAL

(ETHINYL ESTRADIOL)